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The South African Chapter of the IASP

Clinical Practice Guidelines for Management of Neuropathic Pain: expert panel recommendations for South Africa

Case Study: The Backache of Failed Back Surgery Syndrome (FBSS)

Identification and Treatment of Neuropathic Pain in Patients with Cancer

Medication Overuse Headache

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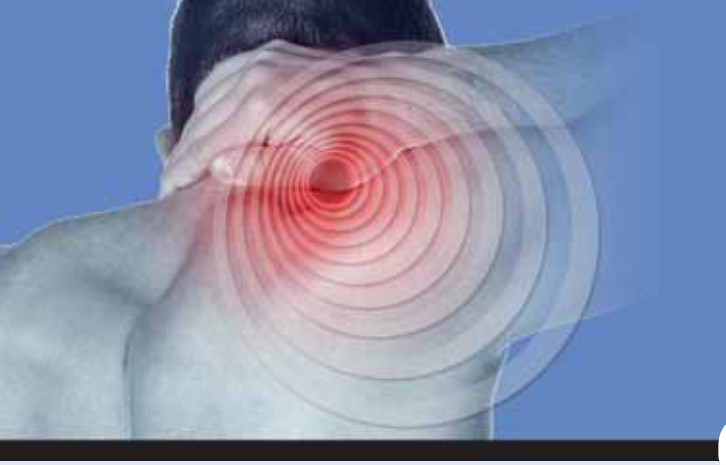

CONGRESS ISSUE 2012

EDITORIAL

The objective of *PAINSA* and the IASP is to improve the management of pain for all patients. This ideal and objective has certainly not been attained in all parts of the world and indeed neither in all parts of our country. The process of improving pain management is a gradual one but each step taken is actually a giant stride for our patients.

PAINSA and its members are at the forefront of pain management in South Africa and it makes me proud to say that the membership of this organisation is steadily growing as is the readership of our *Journal*. This edition will certainly highlight what is being achieved by *PAINSA* and its members.

I must thank the Editor of the SAMJ for his permission to publish the "Clinical practice guidelines for the management of neuropathic pain". This article is a consensus statement by experts in this field in South Africa and includes neurologists, psychiatrists, neuroscientists, orthopaedic and neuro surgeons, rehabilitation specialists, as well as anaesthesiologists. I wish to single out Dr Sean Chetty for coordinating this endeavor and express my thanks and appreciation for his efforts.

Such published articles make it easier for physicians to manage and treat patients with neuropathic pain. *PAINSA* will remain at the forefront of such tasks and a guideline on neuromodulation will soon follow. We can see that the expertise for such undertakings exists in South Africa and the results of these will certainly lead to improvement of pain management in South Africa.

I have also included two local case studies, not only to exhibit the pathology encountered but because these two studies give an excellent overview of their cases and suggested treatment methods. I thank the authors for their submissions and encourage everyone to submit their case reports and articles to the *Journal*.

The majority of this edition is dedicated to the Annual Congress of *PAINSA*. My thanks go to the Chairperson, Dr Sean Chetty and to the head of the Scientific Committee Dr Peter Kamerman. I am sure that those of you who are attending will benefit from the excellent programme and will encourage more of your colleagues to attend future meetings. The abstracts will certainly highlight the high standard of the presentations.

I look forward to meeting with you at the Congress!

Dr Milton Raff
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Clinical practice guidelines for management of neuropathic pain: expert panel recommendations for South Africa

S Chetty, E Baalbergen, A I Bhigjee, P Kamerman, J Ouma, R Raath, M Raff, S Salduker

Neuropathic pain (NeuP) is challenging to diagnose and manage, despite ongoing improved understanding of the underlying mechanisms. Many patients do not respond satisfactorily to existing treatments. There are no published guidelines for diagnosis or management of NeuP in South Africa. A multidisciplinary expert panel critically reviewed available evidence to provide consensus recommendations for diagnosis and management of NeuP in South Africa. Following accurate diagnosis of NeuP, pregabalin, gabapentin, low-dose tricyclic antidepressants (e.g. amitriptyline) and serotonin norepinephrine reuptake inhibitors (duloxetine and venlafaxine) are all recommended as first-line options for the treatment of peripheral NeuP. If the response is insufficient after 2 - 4 weeks, the recommended next step is to switch to a different class, or combine different classes of agent. Opioids should be reserved for use later in the treatment pathway, if switching drugs and combination therapy fails. For central NeuP, pregabalin or amitriptyline are recommended as first-line agents. Companion treatments (cognitive behavioural therapy and physical therapy) should be administered as part of a multidisciplinary approach. Dorsal root entry zone rhizotomy (DREZ) is not recommended to treat NeuP. Given the large population of HIV/AIDS patients in South Africa, and the paucity of positive efficacy data for its management, research in the form of randomised controlled trials in painful HIV-associated sensory neuropathy (HIV-SN) must be prioritised in this country.

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1. Introduction

Neuropathic pain (NeuP) is defined as pain that arises as a 'direct consequence of a lesion or disease affecting the somatosensory system'.[1] Importantly, NeuP differs from nociceptive pain in respect of causes, mechanisms, symptomatology and different therapeutic approaches required for successful management.

The burden of NeuP for the patient is substantial. NeuP is associated with psychological distress, physical disability and reduced overall quality of life.[2-5] A systematic review and meta-analysis by Doth *et al.*[6] showed lower health-utility scores in patients with NeuP than the general population and in people with other chronic conditions like Parkinson's disease, heart failure, motor neurone disease, cancer, and stroke. Patients with peripheral NeuP are generally affected by difficulty in sleeping, lack of energy, drowsiness, and difficulty in concentrating.[7] The problem is further compounded by the fact that globally, and in South Africa, NeuP is often underdiagnosed and inappropriately treated, exacerbating the burden of this already debilitating condition.

The costs of NeuP are considerable,[3,8] with misdiagnosis, mistreatment, and mental and physical comorbidities such as depression and nerve damage contributing to the cost, in addition to usual diagnostic and treatment costs. Indeed, it has been reported that patients with NeuP have annual healthcare costs threefold higher than the costs for matched control populations.[9]

Reduced work ability of patients and carers, and medical expenses also contribute to the overall cost of NeuP.[10] A survey in the USA revealed that almost 65% of working patients with painful diabetic neuropathy reported absence from work or decreased work productivity due to pain.[11] Another study reported that the employment status was reduced, owing to pain, in 52% of patients with peripheral NeuP.[7]

In South Africa there are a number of specific challenges to evaluating and treating NeuP. Lack of education and awareness among physicians, including specialists, was noted as a problem in South Africa, leading to suboptimal identification, assessment and management of NeuP. For example, inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids as first-line treatment is widespread, and inappropriate back surgery is common. Referrals to pain clinicians often come too late, and even in specialist centres a multidisciplinary approach is not always taken.

Patient access to care varies widely in South Africa, from rural to urban areas and across socioeconomic divides. But access to care does not guarantee access to the most appropriate drugs, as financial and supply-chain constraints, and restricted formulary in the public sector and restricted reimbursement in the private sector limit access to appropriate medications.[12] Along with access issues, lack of trained personnel is also a problem.[13,14] Added to these challenges, which are not necessarily unique to South Africa, is the high rate of HIV in this country and the paucity of evidence for treating painful HIV-related neuropathy.[15]

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To improve NeuP management in South Africa, regional guidelines for NeuP management, which take local settings into account, are vital. The consensus recommendations described here aim to help healthcare practitioners in South Africa become more aware of NeuP, better skilled at its diagnosis, and equipped to select appropriate treatment options for patients suffering from NeuP.

2. Methods

2.1 Expert panel

A panel with special expertise in diagnosis and management of NeuP met in Johannesburg, South Africa on 9 July 2011. The panel included specialists from the fields of psychiatry, neurology, neurosurgery, anaesthesiology, family medicine and basic science.

The panel collaborated with a French NeuP specialist to critically analyse available randomised controlled trials (RCTs) and evidence-based international and regional guidelines for the evaluation and treatment of NeuP. The objective of the meeting was to develop clear clinical practice guidelines to aid the diagnosis and medical management of NeuP in South Africa.

2.2 Evidence evaluation

Recommendations from recent international and regional guidelines were reviewed in addition to discussion of recent systematic reviews, meta-analyses, and peer-reviewed randomised, double-blind, placebo-controlled studies;[15-30] a number of Cochrane reviews were also referred to.[31-40] The validity, clinical relevance, and applicability of the evidence for peripheral and central NeuP in South Africa were discussed.

The main sources of evidence were the 2010 guidelines from the European Federation of Neurological Societies (EFNS)[26] and recommendations from both the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP)[27,41] and the French Pain Society,[16] all based on systematic reviews of available evidence. A systematic review of evidence by Danish pain experts,[17] consensus recommendations from the Canadian Pain Society[19] and consensus recommendations from experts in Latin America,[18] the Middle-East region (MER)[21] and the Maghreb region[22] were also consulted. Reference was also made to the American Academy of Neurology (AAN) guidelines for management of painful diabetic peripheral neuropathy (DPN);[20] postherpetic neuralgia (PHN)[24] and trigeminal neuralgia (TN)[23] were also referred to.

It was decided against using number-needed-to-treat (NNT) as the sole measure of efficacy in making recommendations for South Africa, since NNT does not provide a complete picture of the quality of a study, particularly as the studies assessed vary widely in number of participants and quality of study design.

After considering the evidence, the panel achieved consensus on a number of recommendations that are supported by best scientific evidence. The recommendations include some agents that may not be indicated for use in NeuP. Similarly, some agents that are supported by best scientific evidence are not available in South Africa (e.g. the topical lidocaine patch), so are mentioned here but have been excluded from the final recommendations.

The levels of evidence stated in this review follow the levels attributed in the formal systematic reviews from which the data were sourced (refer to Appendix A).

2.3 Guideline development

The discussions and consensus statements were recorded at the meeting and written up as a full manuscript draft by a professional medical writer. The panel reviewed, edited, and provided comments on the outline and drafts of the manuscript until a final version was reached that was approved by all members.

3. Results

3.1 Epidemiology and burden of NeuP

Estimating the prevalence of NeuP is notoriously difficult – a recent systematic review by Smith and Torrence[42] found that estimates vary widely, confounded by underreporting and inconsistent definitions and diagnostic criteria. They suggest a prevalence of 6 - 8% in the general population. They estimate that approximately 20% of patients with diabetes and 8% of people who have had herpes zoster suffer from NeuP.

There are no published estimates of NeuP prevalence in South Africa. The prevalence of NeuP resulting from common aetiologies (see Table 1) is likely to be similar to other countries, but with a large additional component resulting from the high rate of HIV in this country.

Low back pain is a major contributor to NeuP prevalence globally, and there may be a neuropathic component in nearly 50% of black Africans with lower back pain.[43] A similar rate of neuropathic pain (55%) was reported in adults with lower back pain in an outpatient setting in the Arabian Gulf region.[44] PHN and DPN are also leading causes of NeuP, but data on the prevalence of these causes in South Africa are limited. The International Diabetes Federation (IDF) Diabetes Atlas estimates the prevalence of type II diabetes in the Africa region in 2010 to be 3.8%,[45] which is below the global average but expected to rise disproportionately in the developing world in the coming decades.[46] In diabetes patients attending outpatient clinics in the Middle East, 54% met the criteria for painful DPN.[47] The reported occurrence of peripheral neuropathy in patients with diabetes varies widely in sub-Saharan African countries, from 4% in Zimbabwe to 69% in Nigeria,[48] and was estimated at 28% among black African diabetes patients in a 1997 audit of public-sector diabetes care in South Africa.[49] While not all diabetes-related neuropathy is painful, as many as 20% of diabetes patients could suffer from NeuP related to DPN,[42] and this clearly represents a large, and growing, cause of NeuP, in South Africa.

According to the 2010 global report by the United Nations Program on HIV/AIDS (UNAIDS), 5.6 million people in South Africa are living with HIV.[50] HIV-associated sensory neuropathy (HIV-SN), a frequent complication of both HIV and neurotoxic antiretroviral medications such as stavudine, is therefore a major concern in South Africa.

Prevalence of NeuP was reported to be 20.9% among South African AIDS patients who had not received prior antiretroviral treatment.[51] The prevalence of symptomatic HIV-SN was 57% in 395 HIV-positive black South Africans exposed to stavudine, with 76% of affected individuals experiencing pain as their primary symptom.[52] In 598 HIV-infected individuals in South Africa, the frequency of HIV-SN was 37% in individuals never exposed to antiretroviral drugs, increasing to 60% in individuals receiving antiretroviral therapy. In both groups of patients, the neuropathy was symptomatic in approximately 60% of individuals, with almost all these individuals reporting pain and/or paraesthesias.[53]

A recent study conducted in a South African hospital revealed that although 71% of the patients with HIV/AIDS had pain documented in their medical charts, only 34% of the patients reported adequate pain management.[54] HIV-positive outpatients are no better off, with over 40% of ambulatory patients in pain not receiving any treatment, and of those patients who received treatment, less than 3% received drugs recommended for the treatment of NeuP, despite over a third of the patients having symptoms consistent with HIV-SN.[55] These studies highlight that the neuropathic component of HIV-related pain is probably poorly recognised and undertreated in South Africa.

Table 1. Aetiology-based classification of painful peripheral neuropathies

Focal or multifocal lesions of the peripheral nervous system	Generalised lesions of the peripheral nervous system (polyneuropathies)	Lesions of the CNS	Complex neuropathic disorders
Common/important			
Post-traumatic neuralgia Phantom limb and stump pain PHN	Diabetes mellitus (leading to DPN) Alcohol HIV (leading to HIV-SN) Antiretroviral agents Chemotherapy	SCI Stroke	Complex regional pain syndromes types I (controversial) and II
Others/miscellaneous			
Diabetic proximal mononeuropathy Entrapment syndromes Ischaemic neuropathy	Heavy metals, e.g. thallium, arsenic Drugs, e.g. metronidazole, isoniazid, vinca alkaloids Metabolic/genetic, e.g. amyloid, uraemia, Fabry disease Nutritional, e.g. vitamin B deficiencies	MS Syringomyelia Spinal infarction	

Modified from Baron *et al.*[56] CNS – central nervous system, PHN - postherpetic neuralgia, DPN - diabetic peripheral neuropathy, HIV-SN - HIV-associated sensory neuropathy; SCI - spinal cord injury; MS - multiple sclerosis.

3.2 Pathophysiology of NeuP

NeuP, by definition, arises as a 'direct consequence of a lesion or disease affecting the somatosensory system'.[1] While the detailed mechanisms that underlie NeuP are not fully understood, they are thought to operate at both central and peripheral levels (Fig. 1): (A) at the level of peripheral nerves, there is sensitisation, ectopic transmission and spontaneous discharges; (B) changes in central modulatory systems, predominantly in spinal neurones, lead to central sensitisation.

The relationship between these mechanisms and the resulting symptoms is not straightforward – one mechanism may give rise to more than one symptom and one individual symptom may result from multiple mechanisms.[56]

Knowledge of the possible mechanisms underlying NeuP is helpful in understanding and improving treatment of NeuP. An overview of the basic mechanisms and targets for disease is given in Fig. 1.

3.3 Aetiology of NeuP

Currently there is no universally accepted classification for NeuP types. However, four broad classes of diseases are recognised based on aetiology and anatomy (Table 1).

3.4 Clinical features of NeuP

Patients with NeuP experience symptoms arising in an area of altered sensation (numbness/loss of sensation and/or hyperexcitability) and exhibit a number of typical observable signs.[57]

The painful symptoms include both spontaneous pain (i.e. occurs with no apparent stimulation), which can be continuous or paroxysmal, and evoked pain. Terms commonly used to describe painful and unpleasant sensations (dysaesthesias) include burning, shooting, and electric shock-like pain. A number of altered, but not unpleasant, sensations (paraesthesias) – tingling, ants crawling, and pins and needles – are also common. Stimulus-evoked pain is described as allodynia if normally non-painful stimuli (e.g. light breeze, skin contact with clothing, temperature change) evoke pain, and as hyperalgesia when a normally painful stimulus (e.g. pinprick) evokes a heightened pain sensation.[58]

3.5 Diagnosis and evaluation of NeuP

NeuP is distinct from other chronic pain types that have an intact nociceptive system (nociceptive pain). For the differential diagnosis

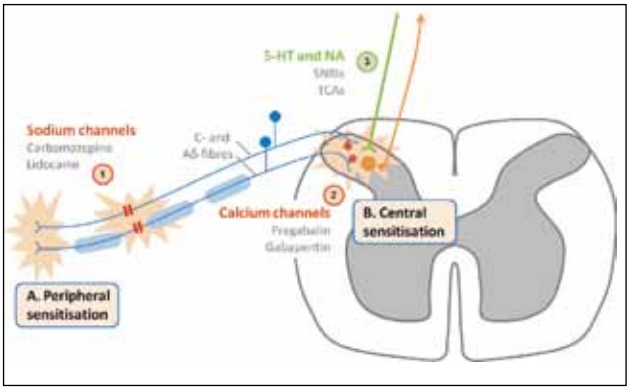

Fig. 1. Lesion of peripheral nerves results in peripheral sensitisation (A), via a number of mechanisms. For example, increased expression of sodium and calcium channels, in unmyelinated (C-fibre) and thinly myelinated (Aδ-fibre) primary afferent neurones can lead to spontaneous discharges, reduced thresholds for activation, enhanced responses to stimuli and abnormal neuronal sprouting (e.g. neuroma formation). This peripheral sensitisation can drive dramatic secondary changes in the spinal cord dorsal horn, leading to central sensitisation (B) – an increase in the general excitability of multireceptive spinal cord neurones. The glutamate NMDA receptor plays a central role in these changes, which are manifested by increased neuronal activity in response to noxious stimuli, expansion of neuronal receptive fields and spread of spinal hyperexcitability to other segments. Dorsal horn neurones receive a powerful descending modulatory control from the brain and brainstem, and dysfunction of the descending inhibitory serotonergic and noradrenergic pathways may contribute to central sensitisation. Each of these malfunctioning systems represents a target for drugs used to treat NeuP: 1. carbamazepine and lidocaine target sodium channel; 2. gabapentin and pregabalin target calcium channels (the $\alpha_2\delta$ subunit) on terminals in spinal neuronal circuits; and 3. serotonin/noradrenaline reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) target descending serotonergic and noradrenergic pathways.

of NeuP it is helpful to analyse the exact quality of somatosensory abnormalities in the affected area as well in the areas adjacent to the sensory deficit.[56] Clinical tools, such as questionnaires for screening and assessment, focus on the presence and quality of neuropathic pain, and can be used to alert a clinician to the likelihood of NeuP and the need for a careful examination. It is important to note that screening tools fail to identify about 10 - 20% of patients with clinician-diagnosed NeuP,[59] and they should be used as a guide for further diagnostic evaluation and pain management but cannot replace clinical judgment.

3.5.1 Screening tools

In recent years, several standardised screening tools have been developed to aid the identification and classification of NeuP on the basis of patient-reported verbal descriptors of pain qualities.[59] These include (among others) painDetect, ID-Pain, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Neuropathic Pain Questionnaire (NPQ) and *Douleur Neuropathique en 4 questions (*DN4). Most of these questionnaires include questions about burning pain, paraesthesias, pain attacks, mechanical and thermal hypersensitivity, and numbness.[60,61] They are attractive because of their ease of use by both professionals and patients, in clinic or via telephone or Internet, and because they provide immediate information.[61]

The painDetect questionnaire was developed and validated in Germany to identify NeuP components in back pain, whereas ID-Pain, DN4 and LANSS were developed to help differentiate nociceptive pain and NeuP.[62,63]

The DN4 scale is based on the patient's description, and physician examination, of sensory dysfunction – it has a sensitivity of 82.9% and specificity of 89.9%.[64] The 10-item questionnaire includes 7 items related to symptoms and 3 related to clinical examination. A total score of 4 or higher suggests NeuP. The 7 sensory descriptors can be used as a self-report questionnaire with similar results. The DN4 has validated translations in 15 languages (in addition to its original French), and while it is not validated in South African languages, the DN4 questionnaire (Fig. 2) is recommended as it is short, quick and easy to follow in regular clinical practice.

3.5.2 Clinical assessment

A simple examination-based way to identify NeuP and differentiate from nociceptive pain is the '3L' approach: Listen, Locate and Look (Table 2).[65]

Listen to the verbal description of pain and any non-painful symptoms in the same area as the pain.

Locate the region of pain and document with a pain drawing, created either by the patient or by the physician. Any abnormal sensations may also be highlighted on the same illustration.

Look for sensory abnormalities and recognise the distribution pattern. A careful inspection of the painful body area should be carried out and any differences in colour, texture, temperature, etc. should be noted. A simple bedside examination of somatosensory functions is recommended, including touch, cold, warmth and pain sensibility (Table 3).[59] The aim is to identify altered sensation in the painful area, and hence responses should be compared with a non-painful adjacent area.

Physicians need to consider a holistic approach to diagnose and treat the underlying condition and comorbid conditions. This will lead to improvement of patients' overall quality of life, physical functioning and sleep quality, along with a reduction of the psychological distress associated with NeuP conditions. Where the underlying pathology is understood, it is recommended that both symptomatic treatment (pain management) and treatment of the aetiology should be initiated. Where the underlying pathology is not clear, symptomatic treatment should be initiated while further testing is done to clarify the pathology.

3.5.3 Recommendations

- Apply screening tools and careful clinical examination and screening tools to help identify and evaluate NeuP.
- Use simple screening tools such as DN4 to help identify likely NeuP.
- Employ the 3L approach to differentiate NeuP from nociceptive pain: **listen** to the verbal description of pain, **locate** the region of pain and **look** for somatosensory deficits with the help of simple bedside tests.

3.6 Pharmacological treatments

Despite a reported 66% increase in published randomised, placebo-controlled trials (RCTs) for NeuP in the past 5 years,[17] there are several gaps in the evidence for NeuP treatments. Although many types of peripheral and central NeuP occur in clinical practice, most RCTs have included patients with either PHN or painful DPN. Importantly, there are very few head-to-head trials comparing different treatments, making direct comparisons of efficacy and tolerability difficult or impossible. HIV neuropathy and chronic radiculopathy seem less responsive to drugs generally found useful in other NeuP conditions based on large-scale trials, particularly tricyclic antidepressants (TCAs), pregabalin, and gabapentin.[15,66] Central NeuP is also difficult to treat, and while it appears to respond to the same drug treatments as peripheral NeuP, the response is generally less robust.[66]

3.6.1 Treatment recommendations by international guidelines

In the past few years, several national, regional and international guidelines, systematic reviews and expert panel recommendations have been published for the treatment of NeuP,[16-19,21,22,26,27,41] and for specific aetiologies;[20,23,24] these are summarised in Table 4a and 4b.

The first-line treatments recommended by most of the guidelines are TCAs, $\alpha_2\delta$-ligands or gabapentinoids (pregabalin and gabapentin), and topical lidocaine (for localised NeuP), with selective serotonin/noradrenaline reuptake inhibitors (SNRIs) sometimes included as first-line, sometimes second-line therapy. All guidelines recommend reserving tramadol and stronger opioid analgesics for second- or third-line treatment (Table 4a).

The EFNS[26] and the French[16] publications provide recommendations separately for specific NeuP aetiologies, while the others make general recommendations for peripheral (and central) NeuP.

3.6.2 Treatment framework

The initial approach to treatment of NeuP should include a thorough investigation and treatment of underlying pathology. The treatment choice should address the possible pain mechanisms as well as comorbid conditions (anxiety, depression, sleep disorders) associated with pain. Other considerations for treatment selection include potential for adverse effects, drug interactions, contraindications, risks of misuse and abuse, patients' response to prior therapy, and cost. Patient education is a vital aspect of NeuP management. It is important to clearly explain the mechanisms of NeuP as well as the goals of treatment to the patient in order to maximise treatment benefits and manage treatment expectations. The patient should be informed that the onset of analgesic effect will take time and reduction of pain is not achieved quickly, in most cases. Non-pharmacological methods of coping with pain should be discussed, including the importance of stress reduction and good sleep hygiene, and access to physical therapy and psychotherapy should be recommended or arranged.

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International Guidelines:
1. US; Postherpetic neuralgia
2. Canada; Chronic NeP
3,4. EU; NeP

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No dosage adjustment is required for patients with hepatic impairment. ***Children*** - Not recommended below the age of 18 years. ***Elderly*** - No dosage adjustment necessary unless renal function is compromised. **Side Effects And Special Precautions:** *Common side effects* - increased appetite, euphoric mood, confusion, decreased libido, irritability, dizziness, somnolence, ataxia, disturbance in attention, abnormal co-ordination, impaired memory, tremor, dysarthria, paraesthesia, blurred vision, diplopia, vertigo, dry mouth, constipation, vomiting flatulence, erectile dysfunction, fatigue, peripheral oedema, feeling drunk, oedema, abnormal gait, increased weight. *Uncommon* - anorexia, depersonalization, anorgasmia, restlessness, depression, depression, agitation, mood swings, exacerbated insomnia, depressed mood, hallucination, abnormal dreams, increased libido, panic attack, apathy, cognitive disorder, hypoaesthesia, visual field defect, nystagmus, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, postural dizziness, hyperaesthesia, ageusia, burining sensation, intention tremor, stupor, syncope, visual disturbance, dry eye, eye swelling, reduced visual acuity, eye pain, asthenopia, increased lacrimation, tachycardia, flushing, hot flushes, dyspnoea, nasal dryness, abdominal distension, salivary hypersecretion, gastro-oesophogeal reflux, oral hypoaesthesia, sweating, papular rash, muscle twitching, joint swelling, muscle cramps, myalgia, arthralgia, back pain, limb pain, muscle stiffness, dysuria, urinary incontinence, delayed ejaculation, sexual dysfunction, asthenia, fall, thirst, tight chest, increased alanine aminotransferase, increased blood creatinine phosphokinase, increased aspartate aminotransferase, decreased platelet count. *Rare* - neutropenia, hypoglycaemia, disinhibition, elevated mood, hypokinesia, parosmia, dysgraphia, photopsia, eye irritation, mydriasis, oscillopsia, altered visual depth perception, peripheral vision loss, strabismus, visual brightness, hyperacusis, atrioventricular block first degree, sinus tachycardia, sinus arrhythmia, sinus bradycardia, hypotension, peripheral coldness, hypertension, nasopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, tight throat, ascites, dysphagia, pancreatitis, cold sweat urticaria, cervical spasm, neck pain, rhabdomyolysis, oliguria, renal failure, amenorrhoea, breast pain, breast discharge, dysmenorrhoea, hypertrophy breast, pain exacerbated anasarca, pyrexia, rigors, increased blood glucose, increased blood creatinine, decreased blood potassium, decreased blood cell count. 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DN4 Questionnaire PATIENT INTERVIEW
Question 1. Does the pain have any of the following characteristics?
1. Burning
2. Painful sensation of cold
3. Electric shocks
Question 2. Is the pain associated with any of the following symptoms in the same area?
4. Tingling
5. Pins and needles
6. Numbness
7. Itching
PATIENT EXAMINATION
Question 3. Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?
8. Hypoaesthesia to touch
9. Hypoaesthesia to prick
Question 4. In the painful area, can the pain be caused or increased by:
10. Brushing
YES = 1 point
NO = 0 points
Patient's score: _____/10 If the patient's score is 4, the test is positive. (sensitivity 82.9%; specificity 89.9%)

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Fig. 2. DN4 questionnaire.

3.6.3 Peripheral NeuP

Four classes of drugs have good evidence of efficacy in the treatment of non-localised NeuP: $\alpha_2\delta$-ligands (pregabalin and gabapentin), TCAs (low-dose amitriptyline or other TCA), SNRIs (duloxetine and venlafaxine), and opioids (tramadol, methadone and morphine).

The efficacy and safety of these agents are briefly discussed below and also summarised in Table 5.

3.6.3.1 $\alpha_2\delta$-ligands (pregabalin and gabapentin)

Pregabalin and gabapentin are recommended (grade A) as first-line therapy

Table 2. 3L approach to differential diagnosis of NeuP[59]

	Listen	Locate	Look
Neuropathic pain	Common descriptors: shooting, electric shock, burning, tingling, itching, numbness	The painful region may not necessarily be the same as the site of injury. Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain)	Apply bedside sensory tests Conduct aetiology-specific tests if appropriate
Nociceptive pain	Common descriptors: aching, throbbing, stiffness	Painful region is typically localised at the site of injury	Physical manipulation causes pain at site of injury

Modified from Haanpaa *et al.*[59]

Table 3. Bedside assessment of negative and positive sensory symptoms and signs in patients with NeuP

Signs and symptoms	Bedside assessment
Negative symptoms and signs	
Tactile hypoaesthesia/numbness	Touch skin with a painter's brush, cotton swab, or gauze
Hypoalgesia	Single pin-prick with a safety pin or sharp stick (e.g. cocktail stick/toothpick)
Thermal hypoaesthesia	Cold (10°C): calibrated metal roller or glass with water, acetone Hot (40°C): calibrated metal roller or glass with water
Evoked pain	
Mechanical allodynia (dynamic)	Stroke skin with a painter's brush, cotton swab, or gauze
Mechanical hyperalgesia (static)	Firm pressure applied with the finger
Mechanical hyperalgesia (punctuate/pin-prick)	Prick with a safety pin, sharp stick, or stiff von Frey hair
Temporal summation	Prick with safety pin or sharp stick at intervals of <3 s for 30 s duration
Cold hyperalgesia (20°C)	Calibrated metal roller, glass with water, acetone Control: objects at skin temperature
Heat hyperalgesia (40°C)	Calibrated metal roller, glass with water Control: objects at skin temperature
Mechanical deep hyperalgesia (somatic)	Apply manual light pressure at joints or muscles

Adapted from Baron *et al.*[56]

by IASP, EFNS, and French guidelines, based on high-quality evidence of efficacy established in multiple RCTs.[16,26,27] The AAN guidelines for painful DPN recommend pregabalin (level A) because of the availability of strong evidence and gabapentin (level B evidence).[20] A systematic review by Danish pain experts[17] and several Cochrane reviews[32,35,67] confirm the efficacy of these $\alpha_2\delta$-ligands for the treatment of NeuP.

Although pregabalin and gabapentin appear to have similar efficacy, there are minor differences in the pharmacokinetic profile of these two drugs.[27] Gabapentin pharmacokinetics are nonlinear (due to saturable absorption), and dosing requires careful titration. Treatment should be initiated at low dosages with gradual increases until pain relief, dose-limiting adverse effects, or a dose of 3 600 mg/day in 3 divided doses is/are reached. Pregabalin has linear pharmacokinetics and dosing is more straightforward. Dosing can start at 25 mg/day (at night), and be titrated slowly up to a maximum dose of 300 - 450 mg/day (in 2 divided doses). Because of its shorter titration period and potentially efficacious starting dosage, pregabalin may provide analgesia more quickly than gabapentin.[27,68] Thus, pregabalin has pharmacokinetic advantages compared to gabapentin.

The IASP NeuPSIG guidelines[16] acknowledge the additional efficacy of gabapentin and pregabalin in sleep disorders, and pregabalin in anxiety disorders associated with pain. Although gabapentin and pregabalin have few drug interactions, both can produce dose-dependent dizziness and sedation, which can be reduced by starting with lower dosages and titrating cautiously. It is also important to note that both these medications require dosage reduction in patients with renal insufficiency.[69,70]

3.6.3.2 SNRIs (duloxetine and venlafaxine)

SNRIs are considered a first-line treatment option by most of the international guidelines, including the NeuPSIG guidelines[27] (grade A) and the EFNS guidelines[26] (level A for DPN), thus highlighting the efficacy of SNRIs for management of NeuP. Although the French guidelines[16] recommend SNRIs for second-line therapy because of the lack of marketing authorisation, duloxetine and venlafaxine have grade A recommendations for DPN and sensory polyneuropathy respectively. Danish pain experts[17] state in their review that duloxetine and venlafaxine have a well-documented efficacy in painful polyneuropathy.

Although both duloxetine and venlafaxine have been studied in peripheral NeuP, especially in painful DPN, more evidence of efficacy is available for duloxetine.[28,30,34,71] Venlafaxine has shown efficacy in painful polyneuropathies of different origins.[31,72] Both duloxetine and venlafaxine are approved for the treatment of major depression disorder (MDD) and generalised anxiety disorder (GAD)[73,74] and hence are the treatment of choice in NeuP patients with these co-morbid conditions. Nausea, the most frequent side-effect with duloxetine, occurs less

Table 4a. Recommended first- and second-line agents for peripheral NeuP by international and national/regional guidelines

	IASP, 2010[27]	EFNS 2010[26]	Latin America, 2009[18]	MER, 2010[21]	FAR, 2011[22]	CPS, 2007[19]	French, 2010[16]	Danish, 2010[17]
First line	Pregabalin Gabapentin SNRIs TCAs Topical lidocaine (localised peripheral NeuP) Tramadol and opioids*	Pregabalin Gabapentin SNRIs (for DPN) TCAs Topical lidocaine (for PHN)	TCAs Topical lidocaine (localised peripheral NeuP)	Pregabalin Topical lidocaine TCAs	Pregabalin Gabapentin Topical lidocaine TCAs	Pregabalin Gabapentin TCAs	Pregabalin Gabapentin SNRI† (duloxetine) TCAs Tramadol (for mixed pain) Topical lidocaine (for PHN with allodynia)	Pregabalin Gabapentin SNRIs TCAs Topical lidocaine (PHN or focal neuropathy with allodynia)
Second line	Opioids Tramadol	For poly-neuropathy: tramadol followed by strong opioids For PHN: opioids and capsaicin	Pregabalin Gabapentin Tramadol (for mixed pain)	SNRIs Opioids (tramadol, oxycodone or others)	SNRI (duloxetine)	SNRIs Topical lidocaine	TCA (maprotiline) SNRI† (venlafaxine) Opioids Tramadol	Tramadol Opioids Combination therapy

* For patients with acute NeuP, NeuP due to cancer, and episodic exacerbations of severe NeuP, as well as when titrating one of the first-line medications if prompt relief of pain is required.
† Venlafaxine is not proposed as first line given the absence of marketing authorisation in France.
IASP – International Association for Study of Pain; EFNS – European Federation of Neurological Societies; MER – Middle East Region; FAR – French-speaking Magreb region; CPS – Canadian Pain Society; SNRIs – serotonin-noradrenalin reuptake inhibitors; TCAs – tricyclic antidepressants; DPN - diabetic peripheral neuropathy; PHN – postherpetic neuralgia.

Table 4b. Recommended agents for specific peripheral NeuP aetiologies (painful DPN and PHN)

	AAN, 2010 (for painful DPN)[20]	AAN, 2004 (for PHN)[24]
Level A/group 1*	Pregabalin	Pregabalin Gabapentin Lidocaine patch Oxycodone or morphine sulphate, controlled release TCAs
Level B/group 2†	Gabapentin Sodium valproate, SNRIs TCA (amitriptyline) Opioids (dextromethorphan, morphine sulfate, tramadol, oxycodone) Capsaicin (topical) Isosorbide dinitrate spray	Aspirin (cream/ointment) Capsaicin (topical) Methylprednisolone (intrathecal)

AAN – American Academy of Neurology; DPN - diabetic peripheral neuropathy; PHN – postherpetic neuralgia; SNRIs – serotonin-noradrenalin reuptake inhibitors; TCAs – tricyclic antidepressants
*Level A recommendation: established as effective, ineffective or harmful (or established as useful/predictive or not useful/ predictive) for the given condition in the specified population (level A rating requires at least two consistent class I studies) (in exceptional cases, one convincing class I study may suffice for an 'A' recommendation if: (*i*) all criteria are met; and (*ii*) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).
*Group 1. Medium to high efficacy, good strength of evidence, and low level of side-effects.
†Level B recommendation: probably effective for the given condition in the specified population (level B rating requires at least one class I study or two consistent class II studies.)
†Group 2. Lower evidence than those listed in group 1, or limited strength of evidence, or side-effect concerns.

frequently if treatment is initiated at 30 mg/day and titrated after one week to 60 mg/day.[75] According to the IASP NeuPSIG guidelines,[41] duloxetine 60 mg once daily appears to be as efficacious as 60 mg twice daily and is associated with fewer side-effects in painful DPN.

SNRIs in general and duloxetine in particular pose a minor to moderate hepatic risk; the use of duloxetine is contraindicated in patients with severe hepatic impairment.[73] Elevated blood pressure and clinically significant electrocardiogram (ECG) changes are associated with patients treated with venlafaxine.[74] Therefore, venlafaxine should be prescribed with caution in patients with cardiac disease and with regular BP monitoring. Venlafaxine should be tapered when treatment is being discontinued as a withdrawal syndrome

Table 5. Summary of recommended therapeutic agents for peripheral NeuP in South Africa

Drug	Dosage	Side-effects	Contraindications/ precautions/drug interactions	Other benefits	Benefits in symptoms of NeuP
$\alpha^2\delta$-ligands					
Pregabalin	Start: 25 mg nocte Titrate: Increase in 25 mg increments every 2 - 3 days (as tolerated) until the patient is taking 75 mg twice daily. The dose can then be increased by 75 mg/day every 3 - 7 days if necessary Maximum dose: 300 - 450 mg/day in 2 divided doses	Dizziness, sedation, peripheral oedema, dry mouth, asthenia	No significant drug interactions Linear pharmacokinetics Dose reduction required in renal insufficiency	Improvement of sleep disturbance Anxiolytic	Effective in continuous pain[16] and mechanical allodynia[16,26]
Gabapentin	Start: 100 - 300 mg at bedtime or 100 - 300 mg 3 times daily Titrate: Requires careful titration Increase by 100 - 300 mg 3 times daily every 1 - 7 days as tolerated Maximum dose: 3 600 mg/day (1 200 mg 3 times daily)	Dizziness, sedation, peripheral oedema, dry mouth, asthenia	Dosage reduction required in renal insufficiency No clinically significant drug interactions	Improvement of sleep disturbance	Effective in continuous pain[16]
SNRIs					
Duloxetine	Start: 30 mg once daily Titrate: Increase to 60 mg once daily after 1 week. Maximum dose: 60 mg twice daily	Nausea/ vomiting, constipation, anorexia, dry mouth, dizziness	Contraindicated in severe hepatic impairment, end-stage renal disease, alcohol abuse, concomitant use of tramadol and MAOIs Low initial doses for mild to moderate hepatic and renal impairment Caution required in patients with history of mania, seizures, acute narrow-angle glaucoma Glucose monitoring required as worsening glycaemic control seen in diabetic patients Drug interactions with tramadol, TCAs, SSRIs and SNRIs. Inhibition of metabolism of drugs metabolised by CYP2D6 Suicide risk (black-box warning, in line with other antidepressants)	Improvement of MDD and GAD	
Venlafaxine	Start: 37.5 mg once or twice daily Titrate: Increase by 75 mg each week Maximum dose: 225 mg/day To discontinue treatment, venlafaxine should be tapered instead of abrupt discontinuation to avoid withdrawal syndrome	Nausea	Caution required in patients with cardiac disease. Risk of hypertension, hence regular blood pressure monitoring required Lower dose may be necessary in patients with renal impairment (GFR = 10 to 70 ml/min) or cirrhosis of the liver Use with caution in patients with history of seizures and history of mania Drug interactions with tramadol, TCAs, SSRIs and SNRIs. Inhibition of metabolism of drugs metabolised by CYP2D6 Suicide risk (black-box warning, in line with other antidepressants)		

Table 5. Summary of recommended therapeutic agents for peripheral NeuP in South Africa (continued)

TCA-amitriptyline	Start: 10 - 25 mg at bedtime Titrate: Increase by 10 - 25 mg/day weekly Maximum dose: 50 - 150 mg/day; median 50 - 75 mg/day	Sedation, dry mouth, blurred vision, weight gain, urinary retention, dizziness	Contraindicated with MAOI use, antihypertensives, patients with myocardial infarction/heart block, untreated narrow-angle glaucoma Use with caution in patients with glaucoma, cardiovascular disease, especially in elderly patients, hyperthyroidism, impaired liver function, epilepsy, urinary retention, prostatic hypertrophy, constipation, mania	Improvement of MDD	TCAs are effective in continuous and paroxysmal pain and mechanical allodynia[16]
Tramadol	Start: 50 mg once or twice daily Titrate: Increase by 50 - 100 mg/day in divided doses every 3 - 7 days as tolerated Maximum dose: 400 mg/day (100 mg 4 times daily); in patients >75 y, 300 mg/day	Nausea/vomiting, constipation, drowsiness, dizziness, seizures	High risk of addiction and abuse, psychomotor impairment possible Use with caution in patients with history of substance abuse, suicide risk, seizure disorder and in elderly patients because of risk of confusion Contraindicated with concomitant use of SSRI, SNRI, TCA	Rapid onset of analgesic benefit	
Strong opioids	Start: 10 - 15 mg morphine every 4 h or as needed (or equianalgesic dosages of other opioids) Titrate: After 1 - 2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed Maximum dose: No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (e.g. morphine at 120 - 180 mg/day, or equianalgesic dosages of other opioids)	Nausea/vomiting, constipation, drowsiness, dizziness	High risk of addiction and abuse, psychomotor impairment possible Use with caution in patients with history substance abuse, suicide risk and in elderly patients because of risk of confusion Contraindicated with concomitant use of SSRI, SNRI, TCA	Rapid onset of analgesic benefit	

Compiled from Martinez et al.,[16] Bohlega et al.,[21] Dworkin et al.,[27] and experts' clinical experience and opinion.
SNRIs = serotonin-noradrenalin reuptake inhibitors; MOAIs = monoamine oxidase inhibitors; MDD = major depression disorder; GAD = generalised anxiety disorder; TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors.

has been described.[76] Antidepressants are generally associated with increased risk of suicide; hence patients should be closely monitored (refer to Table 5 for additional considerations). An additional consideration, when using relatively high doses (120 mg duloxetine, 225 mg venlafaxine), is the risk of precipitating manic episodes in vulnerable individuals.

3.6.3.3 Low-dose TCAs (amitriptyline, imipramine, nortriptyline)

Published international guidelines including the EFNS[26] (level A evidence for DPN and PHN), IASP NeupSIG[27] (grade A), French guidelines (grade A scientific evidence in several aetiologies) as well as the systematic review by Danish experts[17] have documented the efficacy of TCAs for treating a variety of types of NeuP. A Cochrane review[34] that considered data from 17 studies validated the efficacy of TCAs in NeuP.

TCAs are an attractive option mainly because they are inexpensive and have a convenient once-daily dosing. Although TCAs are approved to treat MDD, the analgesic effect is independent of the antidepressant effect, and occurs at a lower dose.[27] Therefore, low-dose TCAs are not the NeuP treatment of choice in patients with comorbid depression. Starting doses of amitriptyline should be low (10 - 25 mg/day), and titrated slowly until pain is adequately controlled or side-effects limit continued titration.

It is important to take into account the potential for drug interactions, especially when amitriptyline is co-administered with drugs that inhibit CYP2D6 enzyme. TCAs are associated with cardiac toxicity and hence amitriptyline is contraindicated in patients who have ischaemic heart disease or an increased risk of sudden cardiac death.[77,78] The MER guidelines[21] recommend a screening ECG before beginning treatment with TCAs in patients over 40 years of age. Amitriptyline should be avoided in elderly patients. Please refer to Table 5 for additional safety considerations.

3.6.3.4 Opioids (tramadol, morphine and methadone)

The IASP NeuPSIG guidelines[27] reviewed several high-quality RCTs that showed the efficacy of opioid analgesics including tramadol in patients with

different types of NeuP and recommend them as second-line agents (grade A), except in certain specific clinical situations in which first-line use could be considered. The EFNS guidelines[26] recommend opioids as second- or third-line agents with level A evidence for DPN and PHN. A systematic review by Danish pain experts[17] also acknowledged the consistent efficacy of opioids in NeuP.

Tramadol is a weak μ-opioid agonist that inhibits the reuptake of noradrenalin and serotonin. It has been shown to reduce pain in DPN and sensory polyneuropathies; although it may be less efficacious than strong μ-agonists.[79] The risk of abuse with tramadol appears considerably less compared with opioid analgesics.[75] The EFNS guidelines[26] cautions the use of tramadol in elderly patients because of risk of confusion and does not recommended tramadol with drugs acting on serotonin reuptake such as selective serotonin reuptake inhibitors (SSRIs). The French guidelines[16] recommend tramadol for treatment of mixed pain (pain with nociceptive and neuropathic components) as it is effective in nociceptive pain.

Cochrane reviews have demonstrated the effectiveness of strong opioids (oxycodone, morphine, and methadone) in different types of NeuP, providing greater pain relief than placebo.[38,80] In head-to-head comparisons, opioids provided at least as much analgesia as TCAs and gabapentin.[81,82] Despite strong evidence of efficacy, most of the international guidelines reserve opioid analgesics as second- or third-line agents mainly because of risk of long-term side-effects and possible opioid misuse and addiction. The IASP NeuPSIG guidelines estimate that the frequency of these problems associated with opioid analgesics ranges widely from less than 5% to as much as 50%. Hence, prior to initiating opioids, clinicians should take into account the risk factors for abuse, which include active or previous substance abuse and family history of substance abuse.[75]

3.6.4 Recommendations for peripheral NeuP

The panel reviewed the evidence and constructed a treatment algorithm (Fig. 3) to aid step-wise management of non-localised NeuP.

3.6.4.1 First-line treatment

Three classes of drugs are recommended for first-line monotherapy: $\alpha_2\delta$-ligands (pregabalin or gabapentin), TCAs (low-dose amitriptyline or other TCA) and SNRIs (duloxetine or venlafaxine). Pregabalin is the preferred first-line option because of its simple pharmacokinetics and good tolerability. The choice of drug also depends on additional factors summarised in Table 5.

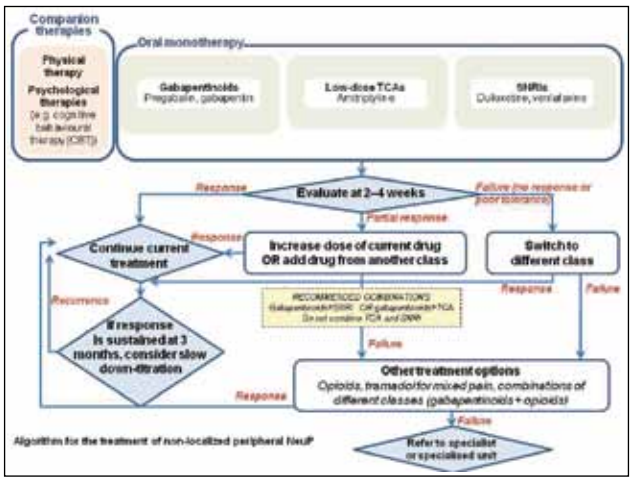

Fig. 3. Algorithm for the treatment of non-localised peripheral neuropathic pain.

Patients should be evaluated at 2 - 4 weeks after initiating therapy to determine response to treatment. If the response is good, the current treatment should be maintained, and if the response is sustained for 3 months, slow down-titration can be attempted. If symptoms return, treatment should be titrated back to an effective dose. If a partial response is seen at 2 - 4 weeks, consider increasing the dose of the current agent. If the response is poor, or the drug is not tolerated, move to second-line approaches.

3.6.4.2 Second-line therapy – combination

In case of partial response to first-line therapy, recommendations include either increasing the dose of the current drug or adding a drug from a different class. In case of complete failure to first-line therapy, the patient should be switched to a drug from a different class.

For combination treatment, pregabalin with either an SNRI or amitriptyline is recommended. It is important to note that although TCA and SNRI are different classes of antidepressant they target the same mechanism, so a combination of SNRI and TCA is not recommended.

Combination therapy may offer additional analgesic benefits and benefits on associated symptoms,[83] but potential advantages must be weighed against the possibility of additive adverse effects, drug interactions, increased cost, and reduced adherence to a more complex treatment regimen.[41]

3.6.4.3 Third-line treatment

If the patient does not respond to combination therapy or the switch strategy, tramadol is recommended (especially in NeuP with a nociceptive component) followed by strong opioids (e.g. morphine, oxycodone, hydromorphone), or a combination of first-line options with opioids.

Evidence for these combinations is limited, but the combination of morphine and gabapentin seems to provide better pain relief than each drug given alone.[82] In another study, a combination of gabapentin and an opioid was associated with significant pain relief and improved sleep, without an exacerbation of opioid-induced adverse events.[84]

3.6.4.4 Follow-up

The tools and scales used for diagnosis may be useful for clinical monitoring (though not all are validated for this use) to establish a baseline and assess the patient's response. Monitoring for potential drug interactions, adverse events, co-morbidities, need for dose titration, etc., should be part of the follow-up plan.

If a patient does not show a satisfactory therapeutic response, he/she should be referred to a pain specialist centre.

3.6.5 Aetiology-based recommendations

3.6.5.1 Polyneuropathy

Painful DPN: The EFNS guidelines[26] recommend the use of TCAs, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) as first-line treatment in painful polyneuropathy (notably related to diabetes), tramadol as second-line therapy and strong opioids as third-line agents.

Recommendations: The panel recommends use of pregabalin or gabapentin, low-dose amitriptyline (or other TCA), duloxetine or venlafaxine (SNRIs) for treatment of painful polyneuropathies, including painful DPN. If response to treatment is poor, patients should be switched to, or have added, a drug from a different class. Tramadol and opioids are recommended after failure of second-line or combination therapy.

Painful HIV-SN: A recent systematic review of pharmacological treatment of HIV-associated neuropathy[15] identified only 3 agents

with good evidence of efficacy (v. placebo): smoked cannabis (1 - 8% δ-9-tetrahydrocannabinol), high-dose topical capsaicin (8%), and recombinant human nerve growth factor (rhNGF). Lamotrigine had limited efficacy in one trial, demonstrating superiority over placebo in a secondary endpoint and only in patients exposed to neurotoxic ARVs.[15] Drugs that are generally effective for peripheral neuropathic pain of other aetiologies (amitriptyline, pregabalin, and gabapentin) have been studied but with no evidence of efficacy, and there have been no RCTs of SNRIs in HIV-associated neuropathy.

Recommendations: Because of the lack of evidence for treatment of HIV-SN, the panel recommends following the framework outlined for other polyneuropathies and the step-wise management as illustrated in Fig 3. In addition, if the onset of the neuropathy is associated with starting antiretroviral therapy (even if it is a tenofovir-based regimen), then an alternative regimen should be considered, where possible.

3.6.5.2 Postherpetic neuralgia

Systematic reviews including a review by the AAN concur that gabapentin, pregabalin, TCAs, lidocaine patches and strong opioids have strong evidence of efficacy in PHN.[24,29,34] Opioids have similar or slightly better efficacy compared with TCA but are associated with more frequent discontinuation because of side-effects.[26,29] Because of the lack of RCTs, the efficacy of SNRIs duloxetine and venlafaxine for the treatment of PHN is not known.

The EFNS guidelines[26] state that although topical lidocaine patches are effective for the treatment of PHN with brush-induced allodynia, the level of evidence is lower compared with systemic agents.[85] Topical capsaicin has also reported modest benefits in patients with PHN.[29]

Recommendations: The panel recommends pregabalin, gabapentin or amitriptyline for first-line treatment of PHN, and to combine drugs from different classes as a second-line approach. Opioids (tramadol, then stronger opioids) should be reserved for third-line treatment.

As a topical lidocaine patch is not available in South Africa, the panel could not recommend its use despite strong supporting evidence. Topical capsaicin is also not available in South Africa, so it cannot be recommended. The panel suggests that the regulatory authorities in South Africa consider approval of these agents for use in neuropathic pain.

3.6.5.3 Trigeminal neuralgia (TN)

The AAN-EFNS guidelines for TN[23] recommend carbamazepine (200 -1 200 mg/day) as the drug of choice in classic TN because of its robust treatment response; however, its efficacy may be compromised by poor tolerability and pharmacokinetic interactions.[23,37] Oxcarbazepine has shown similar efficacy to carbamazepine for controlling pain in TN,[23,26] but with fewer drug-drug interactions. The AAN-EFNS guidelines also comment on the lack of evidence for treatment of TN following failure of first-line therapy and acknowledge some evidence supporting add-on therapy with lamotrigine or a switch to baclofen, but recent Cochrane reviews conclude that there is insufficient evidence to recommend them in TN.[36,39]

Recommendations: The panel recommends the use of carbamazepine and oxcarbazepine for the treatment of TN.

3.6.6 Central NeuP (CP)

Relatively few RCTs have been conducted in patients with CP, but results and clinical experience suggest that such conditions may be relatively more refractory to treatment than peripheral NeuP.[27]

The EFNS guidelines,[26] IASP NeuPSIG group recommendations,[27] and a systematic review by Danish pain experts[17] assessed the available data and agreed that the use of pregabalin, gabapentin, and TCAs (specifically amitriptyline) is best supported for CP states, specifically spinal cord injury (SCI) and poststroke pain. The EFNS guidelines[26] recommend these three agents as first-line options for CP, with tramadol or stronger opioids as second-line. Cannabinoids are suggested in multiple sclerosis (MS) if other treatments fail,[26,27] although poor availability and concerns about risk of abuse and precipitation of psychosis limit use. There is some mixed evidence for lamotrigine in SCI and post-stroke pain.[26, 27]

A systematic review of evidence by Danish pain experts did not include any RCTs with SNRIs in CP.[17] A recent RCT which evaluated the effects of duloxetine on pain relief concluded that there is insufficient evidence for the efficacy of duloxetine in treatment of CP.[86]

Recommendations: Based on the scientific evidence and added benefit in treating comorbidities (depression, insomnia, anxiety), the panel recommends using pregabalin or amitriptyline for first-line treatment of CP (Fig. 4). As a result of the consistent clinical experience, fewer contraindications and better risk/benefit ratio compared with TCAs, the panel agrees that pregabalin should be the preferred option. Treatment trials should be approached as for peripheral NeuP; switching to other first-line agent or combining drugs if treatment fails. Tramadol should be considered next, followed by stronger opioids. As cannabinoids are not available in South Africa they cannot be recommended.

3.7 Non-pharmacological treatments

3.7.1 Companion treatments

A recent review of the evidence supporting the potential complementary role of psychosocial treatments of patients with chronic pain suggest that a combination of psychological, pharmacological and physical therapies, tailored to the needs of the individual patient, may be the best approach.[87] Transcutaneous electrical nerve stimulation (TENS) is widely used for NeuP and nociceptive pain, and while it lacks robust efficacy data,[88] it is recommended by EFNS Task Force[89] as a preliminary or as an adjunct to analgesic therapy as it is inexpensive, non-invasive, safe, and can be self-administered. A review of non-pharmacological treatment approaches by Guastella *et al.*,[90] indicate TENS in focal neuropathic pain when upstream stimulation is possible for a superficial sensitive nerve trunk. There are no good data supporting the use of acupuncture in NeuP.

Recommendation: The panel recommends the use of psychotherapy, particularly cognitive behavioural therapy, and TENS alongside appropriate physiotherapy and pharmacological

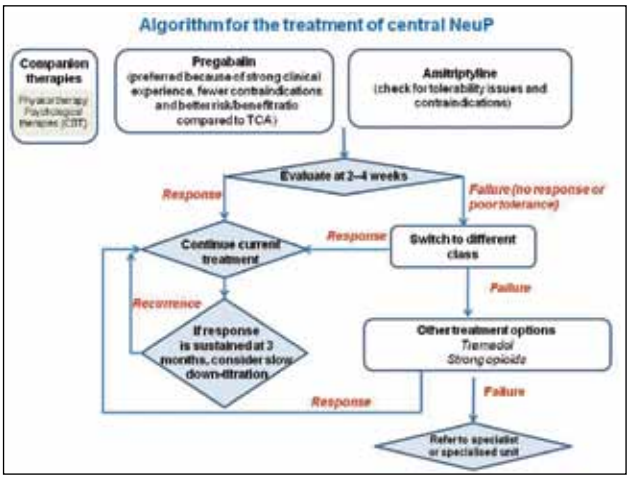

Fig. 4. Recommendations for management of central neuropathic pain.

treatment, for the management of NeuP. Comprehensive patient education can also help improve treatment outcomes.

3.7.2 Stimulatory treatments and surgical management (non-invasive and invasive)

Non-invasive electrical stimulation of the brain, using a variety of methods, has been studied in some chronic pain conditions with very limited evidence of efficacy.[91]

Spinal cord stimulation, via electrodes implanted into the spinal cord, has limited evidence of efficacy in failed back surgery syndrome and complex regional pain syndrome type I,[90] the EFNS Task Force identified level B evidence of efficacy in several systematic reviews, as well as primary studies for spinal cord stimulation in these two conditions.[89] Guastella *et al.*[90] suggest the use of spinal cord stimulation in segmental mononeuropathies refractory to drug treatment.

Dorsal root entry zone lesioning (DREZotomy) involves destruction of nociceptive fibres and the dorsal root entry zones in an aim to destroy the neurones that sustain the painful state. Guastella *et al.*[90] suggest its use in refractory pain due to plexus avulsion.

Recommendations: The panel did not discuss these non-pharmacological treatment approaches extensively, but recommends spinal cord stimulation in cases of pain that cannot be managed by pharmacological and companion treatments. The panel does not recommend DREZotomy for management of any NeuP, because of limited evidence and risk of worsening of NeuP after this invasive procedure.

4. Discussion

The management of NeuP is challenging, and even when NeuP is diagnosed and treated according to the best evidence available, not all patients can achieve a satisfactory response. This article provides recommendations for the management of NeuP in South Africa, with the aim of raising awareness of NeuP and improving its diagnosis and treatment in this country. These recommendations apply published, international, evidence-based guidelines for NeuP management to the South African setting.

NeuP is widely underdiagnosed in South Africa, and the panel recommends the use of simple questionnaires, such as DN4, to identify NeuP. A raised awareness of common signs and symptoms of NeuP, and of the descriptors used by patients, will also help clinicians to better identify those patients who have neuropathic aspects to their pain.

For management of peripheral NeuP, the $\alpha_2\delta$-ligands pregabalin and gabapentin, low-dose TCAs, and the SNRIs duloxetine and venlafaxine are recommended as first-line options. Pregabalin is the preferred option, based on tolerability and pharmacokinetics. Opioids should be reserved for later use, and only after switching to another monotherapy or combination therapy with multiple first-line agents fails.

For painful DPN, recommendations are as for peripheral NeuP in general; for PHN, first-line recommendations are pregabalin (preferred), gabapentin and low-dose amitriptyline; and for TN, oxcarbazepine (preferred) and carbamazepine. Some agents with good evidence, recommended in guidelines from other regions, are not available in South Africa. The panel requests that the South African regulatory authorities evaluate the evidence for the lidocaine patch and topical capsaicin in localised peripheral NeuP and consider approval of these agents in South Africa.

Based on current international recommendations, the committee cannot recommend specific therapy for the management of HIV-associated neuropathy. Currently these patients should be managed following the same recommendations used for the management of peripheral neuropathic pain.

Evidence in CP is less consistent than for peripheral NeuP, but first-line recommendations are pregabalin (preferred) and amitriptyline.

Companion therapies, such as cognitive-behavioural therapy (and other psychotherapy) and physical therapy are recommended to accompany pharmacological management. Invasive options like DREzotomy are not currently recommended.

The recommendations presented here have several limitations. Evidence is still lacking for the relative efficacy of agents for NeuP, as there are very few head-to-head trials. There are also limited data available for pain due to specific aetiologies other than painful DPN, PHN, and TN. In particular, the paucity of evidence for treatment of painful HIV-SN makes it impossible to provide an evidence-based recommendation for this problem that is so common in South Africa. This must be a priority area of future research. In addition, because there are few placebo-controlled RCTs in South African populations, the recommendations given here have to assume that results in other populations can be extrapolated to the various ethnic groups represented in South Africa.

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Appendix A. Evidence classification scheme, and levels of recommendation used by Attal *et al.*[92]

Class I: An adequately powered prospective, randomised, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective, randomised, controlled clinical trials with masked outcome assessment in representative populations. The following are required:

(a) randomisation concealment

(b) primary outcome(s) is/are clearly defined

(c) exclusion/inclusion criteria are clearly defined

(d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias

(e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets

(a) - (e) above or a randomised, controlled trial in a representative population that lacks one criterion (a) - (e).

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Rating of recommendations

- Level A rating (established as effective, ineffective, or harmful) requires at least one convincing Class I study or at least two consistent, convincing Class II studies.
- Level B rating (probably effective, ineffective, or harmful) requires at least one convincing Class II study or overwhelming Class III evidence.
- Level C rating (possibly effective, ineffective, or harmful) rating requires at least two convincing Class III studies.

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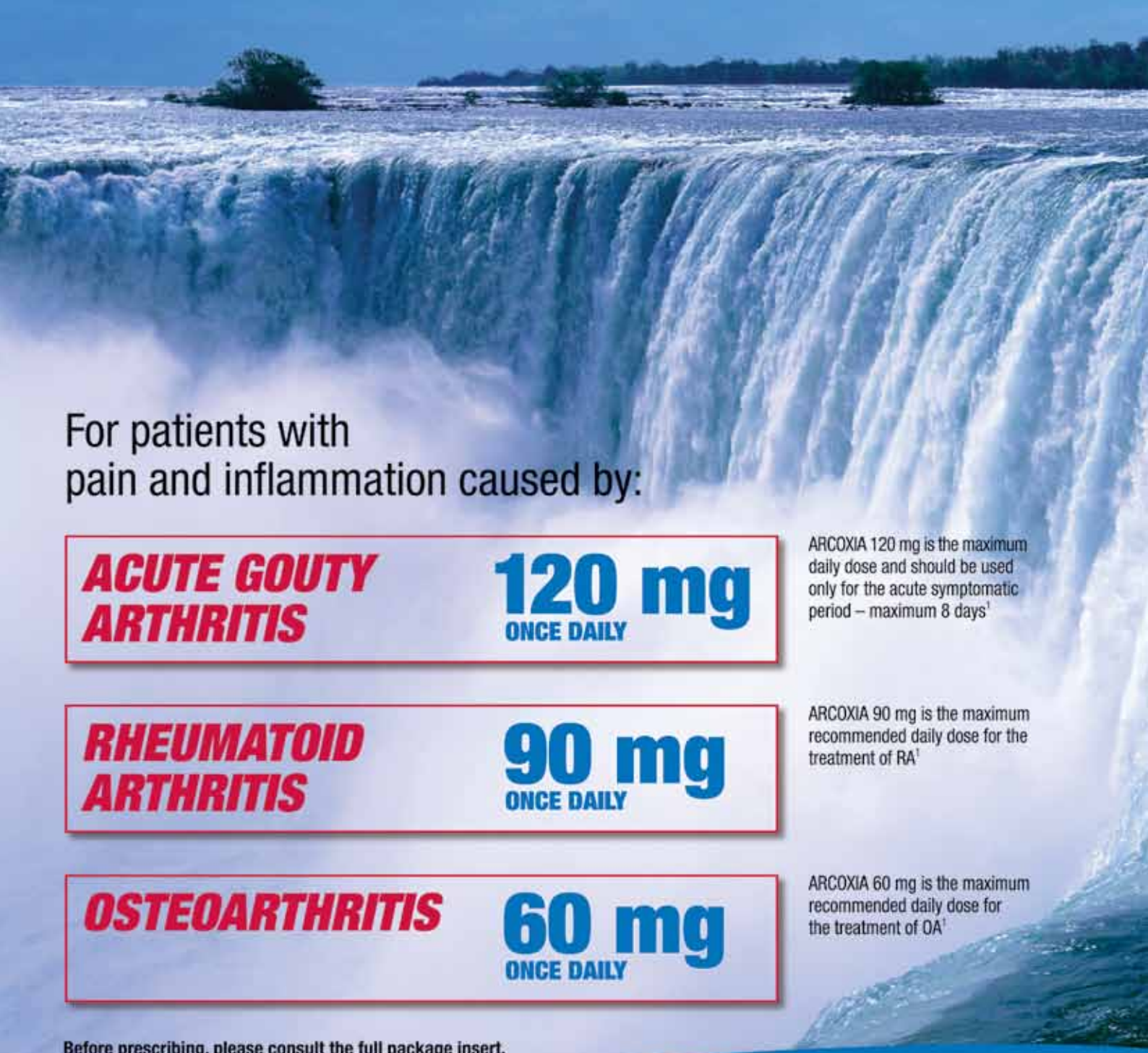

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The backache of Failed Back Surgery Syndrome (FBSS)

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Keywords: back pain, previous back surgery, mixed pain syndrome

Abstract

This case study describes the management of a patient with pain due to "failed back surgery syndrome" (FBSS). The complex etiology and management of FBSS are discussed.

Case Presentation

Mrs CB is a forty-nine year old trained nursing technician who 20 years ago slipped and fractured her fourth lumbar vertebra at work. She consequently needed multiple surgeries. Initially, she had a back fusion from lumbar levels 2 to 5. The following year she had a revision and 4 years later she had a further procedure to remove gauze left from the previous surgery. Later that year she had a screw reinserted and 8 years following this she had a laminectomy with further insertion of screws and plates.

She was referred to our Pain Management Unit 20 months ago. She complained of chronic back pain for 2 years which radiated down her legs. For pain relief she used paracetamol and codeine combinations, amitryptilline and piroxicam. She wore a corset with little analgesic success.

The nature of the pain was of a pricking, sharp and burning quality. She had cramps and "pins and needles" down her legs with associated feet numbness. She was unable to stand for a long period of time. Pain was continuously present but was better in the morning, and worse in the evening. Socially, Mrs CB was separated from her partner for 10 years and the sole bread winner for her three children. Due to her disability she was unable to work.

At the first appointment she reported her verbal numerical scale as 6/10 with her best in the last 24 hours as 2/10. On examination her body mass index (BMI) was 39. On back inspection there was a midline non-hypertrophic scar with non dermatomal hypoanalgesia present. Her range of movement on extension was restricted and painful; she had full but painful range of movement on rotation. There was a sensory and motor deficit present. There was a patchy loss of sensation on her lower limbs and dorsiflexion was absent. A straight leg raising test was negative.

A magnetic resonance image (MRI) showed that her lumbar spine had a Grade 1 anterodisthesis of the fourth over fifth lumbar vertebrae; the lumbar four and five vertebrae had facet joint hypertrophy. Spinal canal stenosis was present. The interpedicular screws were positioned adequately in the fourth and fifth lumbar vertebrae. There was a normal lumbar lordosis.

The working diagnosis was FBSS with associated radiculopathy.

A multidisciplinary approach was applied to Mrs CB's management. This included physiotherapy, group therapy sessions and psychotherapy. Mrs CB was educated about chronic pain and was encouraged to lose weight and to exercise. She was asked to keep a pain diary. Pharmacological treatment was modified to that listed in Table I.

Table I: Pharmacological treatment prescribed for Mrs CB

- Amitryptilline 25mg tablets which were increased to 50mg nightly
- Gabapentin increased gradually to 600mg 8 hourly orally
- DoxypheneR 2 capsules 6 hourly orally
- Baclofen 10mg tablets 6 hourly orally
- Lactulose orally as required

Interventional procedures consequently performed are listed in Table II.

Table II: Interventional procedures performed on Mrs CB

- Facet medial branch nerve block at L4-5 facet joints done 1 month after presentation
- 3 months later she had neurolysis (Racz's technique) performed which resulted in a 5 month pain free period

However her pain returned and after 12 months from her first presentation her verbal numerical scale was 5/10.

Due to exercise and a correct diet plan, Mrs CB managed to lose 20 kg. She became a motivational speaker for people with back pain and speaks at her church meetings and group therapy sessions. She still attends pain clinic and is satisfied with her pain management.

This is a classical presentation of FBSS with radiculopathy. The chronic low back pain presented post spinal surgery was unlike any type of back pain felt prior to surgery. The spinal surgery had corrected all amenable anatomical pathology.

Discussion on FBSS

FBSS is a term involving a group of conditions.[1] It is defined as recurrent or persistent back and leg pain following anatomically successful lumbosacral spine surgery. [1,2,3] Functionally FBSS results when the lumbar spinal surgery fails to meet the pre-operative expectations of the surgeon and patient.[1]

Epidemiology

In the general population FBSS appears to have a reported point prevalence of 0.61%.[3] Spinal fusion surgery increased by 220% between 1990 and 2000 despite no proven efficacy.1 Despite proper surgery, up to 30% of patients fail to improve, as shown by post-operative persistent or recurrent back pain with or without leg pain.[2,4] Recent studies show a failure rate for lumbar spinal fusion of approximately 30% - 46%. The failure rate for microdiscectomy is less (19 – 25%).[1] FBSS patients with severe neuropathic pain experience a lower quality of life and greater disability with a higher unemployment rate.[1, 2, 3,4] Mechanical low back pain was determined to be one of the top five most expensive conditions for employers in the United States.[1] FBSS is a frequent and significant social and economic burden.[1,2,4]

Aetiology

Factors resulting in the syndrome can be practically divided into three categories.[1,2]

Pre-operative factors include patient factors. These are psychological, such as depression and somatization. And social for example personal injury and work compensation claims.

Intra-operative factors include surgical factors, such as inappropriate patient and procedure choice.[1,2,4] A wrong level approach has a reported 2.1-2.7% incidence and an unrecognized incorrect level of operation of 0.57 – 0.72% incidence.[1]

Post-operative factors include surgical complications, for example pseudoarthrosis, haematoma and infection.[1,2,4] Nerve root injuries can result in the "battered root syndrome". Arachnoiditis and persistent epidural fibrosis can theoretically cause tethering of nerve roots and vascular hypoxia leading to persistent pain.[1,2,4] In one review epidural fibrosis is mentioned to be responsible for the FBSS pain in 36% of cases.[1] In other reviews the impact of fibrosis in persistent pain is controversial.[2,4] Progressive disease can involve spondylolisthesis and recurrent disc herniation. The 'Transition Syndrome' involves altered biomechanics from surgery and accelerates preexisting disc degeneration and sacroiliac joint pathology, this occurs in up to 36% of patients following lumbar spinal fusion.[1] Other postulated mechanisms are foraminal, lateral spinal stenosis and 'vertical stenosis', the settling of articular facet joints into a new position compressing nerve roots and a 'micromovement theory'. This has been the identified pain source in 15 to 45% of patients with chronic low back pain.[1,2] Finally, the development of myofascial pain and the possibility of developing 'fusion disease'.[1,2] Myofascial pain syndromes are considered to be due to the 'energy crisis theory'.[4]

Pathophysiology

FBSS is a complex pain syndrome involving mixed neuropathic and nociceptive elements, with occasional sympathetic nervous system involvement. Pain may be visceral and/or somatic in origin.[2] Nerve lesions may trigger molecular changes in somatosensory neurons.[2] Multiple factors – biological, psychological and social – are involved with pain development.[1,3]

Assessment

Van Buyten et al comment that FBSS is easy to recognize but difficult to define.[2] FBSS requires an interdisciplinary approach.

History

A comprehensive history is required with emphasis on:

1) Pain

One must determine the onset and time course for the reappearance of pain.[1] It is important to distinguish between the character and distribution of pain present pre and post operation. Pre-operative persistent symptoms may be caused either by root lesions, resulting in dorsal horn dysfunction or by incomplete surgery. In contrast, post-operative pain may be due to post-operative fibrosis with pressure on and tearing of the roots or intra-operative nerve damage. Rarely, increased post-operative pain has been caused by dislodged or incorrectly placed hardware.[2] In the majority of patients pain progressively worsens slowly for at least 6 months after surgery.2 The predominant site of pain should be noted either low back (axial) or leg (radicular).[1] Mainly axial pain is suggestive of facet and sacroiliac joint degeneration, myofascial or discogenic causes. Radicular pain is likely due to inadequate decompression, epidural fibrosis, recurrent disc herniation, foraminal stenosis or residual disc fragments.[1]

2) Red flags should be sought

These are infectious processes, inflammatory processes, malignancy, new focal neurological deficits and extra-spinal life-threatening causes of back pain for example aortic aneurysms.[1,2] If present; urgent investigations such as a gadolinium-enhanced magnetic resonance imaging (MRI) should be done and definitive treatment undertaken.[1]

2) Yellow flags should be noted

These are psychosocial risk factors, including psychological stressors and exploitation of medical services.[2]

3) Previous surgical assessments and treatment should be reviewed.[1]

This should include pharmacological and non-pharmacological modalities, their efficacy and the treatment's adverse effects and assessment of addiction and drug abuse risk.[1]

Examination

This serves two purposes. Firstly, it assists in ruling out serious pathology in other systems and secondly, to attempt to identify the pain source. This involves the general inspection of posture, gait and function. Indentations and step-offs of the lumbar spine suggest spondylolisthesis. Muscle power is examined with resistance testing. Nerve tension is assessed with the femoral stretch test and Laseuge's signs. Sacroiliac joint (SIJ) pain provocation maneuvers have little accuracy. Waddell's signs are controversial; with some experts suggesting their presence as indicative of psychological distress.[1]

Investigations

Imaging for diagnostic re-evaluation should be performed.[2] These diagnostic tools include X-rays, MRI scans, CT scans and myelograms (if MRI scans are contraindicated). Markers of infection should be done if constitutional symptoms are present. Electrodiagnostic studies are useful in distinguishing other causes of neuropathic pain only.[1] Diagnostic blockades are performed for predominantly axial pain. This is to determine if the pain is due to facet joint pain or the SIJ. [1] These are listed in Table III.[1]

Table III: Diagnostic blockades

1. Lumbar facet medial branch blocks with local anesthetic. These are performed under fluoroscopic guidance. They are target specific for diagnosing facet joint pain.
2. SIJ blockade to determine SIJ pain.
3. Selective nerve root blocks are done under imaging guidance to ensure accurate lumbosacral spine level and placement of medication. This avoids inadvertent intravascular or intrathecal injections.

Transforaminal injections of local anesthetic and corticosteroids may assist in the diagnosis of the radicular pain source at a certain spinal level. They may also help determine whether surgery might be beneficial for pain associated with a herniated disc.

4. Provocative lumbar discography is to improve diagnosis of the disc as the pain generator, which occurs in up to 21.5% of patients. However it is neither accurate nor the gold standard for diagnosing discogenic pain.

Treatment

The most conservative and appropriate surgery should be performed on a suitable candidate.[1] The patient must be well informed and educated on the probable success rate outcome before surgery and an informed decision by the patient must be made.[1] Psychological interventions should be implemented if pre-operative psychological and social stressors are identified.[1] Patients with rapidly progressive radiculopathy and cauda equina syndrome should be referred for urgent surgery.[4]

Treatment guidelines for patients with FBSS are limited due to the paucity of quality clinical trials assessing treatment responses.[1] An organized and intensive interdisciplinary approach is needed with

individual consideration.[1,2] Management objectives are directed to improve functional and coping ability and quality of life.1 Education and cognitive behavioral therapy (CBT) should be employed.1 Below are current treatment options for patients with FBSS.[2]

Conservative Medical Management (CMM)

Lumbar radiculopathy improves within 3 months with conservative medical management in 75% of patients.[1,4] There is no one superior pharmacological agent due to the complex benefit to harm profiles for each medication.[1] If a partial response is elicited to monotherapy a combination regime could be synergistic. Drugs that are used in the treatment of FBSS are listed in Table IV.

Table IV: Classes of pharmacological agents used in the treatment of FBSS1

- Paracetamol
- Non-steroidal anti-inflammatory agents - note this has an unfavorable side-effect profile for long-term use
- COX-2 inhibitors
- Tramadol
- Muscle relaxants
- Antidepressants - tricyclic antidepressants if a neuropathic component is present
- Anti convulsants - there is strong evidence for their efficacy in the neuropathic component of pain, especially gabapentinoids
- Opioids – there is controversy regarding efficacy, side effects and stigma of addiction. A study documented analgesic related deaths as 31% of all deaths following lumbar fusion surgery. Long acting agents should be used. Methadone is emerging as a popular analgesic medication used in the management of chronic non-cancer pain. Advantages are; lower affinity for the mu-receptor, which may result in fewer mu-receptor related side effects (such as constipation), lower risk of opioid – induced tolerance and a possible effect on neuropathic pain that may be related to the N-methyl-D-aspartate receptor antagonist activity of the d-isomer and lack of active metabolites

Interventional management options

These can be considered once the pain source is determined.

1. Facet medial branch blocks and radiofrequency (RF) neurolysis

This is for facet joint pain. Reliable diagnosis may be drawn from the response to medial nerve branch blocks. Criteria for a positive response is at least 80% relief following two concordant blocks. In patients with a positive response, RF neurotomy may produce more sustained analgesia. In the appropriate candidate and with the correct technique used at 12 months follow-up, 60% of patients will have at least 90% pain reduction, while 87% of patients will have greater than 60% pain relief. [1]

2. Epidural steroids

Corticosteroids' mechanism of analgesic action is proposed to include an anti-inflammatory effect, sodium channel blockade and reducing vascular permeability. They have shown to be effective for epidural fibrosis, spinal stenosis, disc disruption and herniation.[1]

3. Percutaneous epidural adhesiolysis

This can be considered if an epidural injection is unsuccessful. This aims to reduce epidural fibrotic tissue and improve delivery of epidurally administered drugs to the target tissue. It is predominantly used for radicular pain but is effective for disc disruption and herniation, epidural fibrosis and spinal stenosis. The risk of dural puncture is 20% due to the patients' anatomical disruption, therefore fluoroscopic guidance is advised.[1]

4. Intrathecal drug delivery systems

These are recommended in patients where all other viable options have failed.[1,4] There is no long-term evidence for these devices. Side effects reported include urinary retention, constipation, equipment malfunction and catheter tip granulomas. Tolerance to opioids and the need for increasing the medication dosage is also a problem with long-term use.[1]

5. SIJ blockade

If SIJ pain is present this reduces persistent low back pain.[1]

Other modalities

Other modalities include physiotherapy and exercise therapy. This improves posture and stability, improves fitness and reduces mechanical stress on the spinal structures. Unfortunately there is little evidence for the added value of physiotherapy.[2] Myofascial trigger points can be considered in refractory cases.[4] Transcutaneous electrical nerve stimulation (TENS) has inadequate evidence for effectiveness.[1] Other modalities used are 'back school', massage, acupuncture, yoga, inferential therapy and spinal manipulation.[1]

Surgical Intervention

Results of further surgical intervention in patients with FBSS primarily associated with back pain are less successful than for patients with predominant complaints of lower extremity pain and therefore rarely indicated.[2] Revision surgery's success rate in FBSS after re-operation is low and 20% have a worsened outcome.[2,4] The initial spinal surgery success rate exceeded 50% but was reduced to 30% after a second surgery and to 5% after the fourth.[1,4] Reoperation should only be considered for FBSS patients whose pain can be attributed to a clearly defined and surgically correctable lesion by an expert spine surgeon.[1,2] Evidence has shown that patients with more than 3 months of radicular pain from a herniated lumbar disk and who have surgery have improved functional and pain outcomes in the short term compared with medical management.[1]

Spinal cord stimulation (SCS)

SCS is thought to provide analgesia via the gate control mechanism and modulation of excitatory and inhibitory neurotransmitter release in the dorsal horn.[1] Studies have demonstrated analgesic and functional benefits in FBSS patients with radicular pain.[2] Currently there is no evidence that SCS is effective for FBSS where the back pain is predominantly axial. The demonstrated efficacy for SCS in randomized control trials makes this a better option than revision surgery. Interestingly, depression was identified as a major factor reducing efficacy of the spinal cord stimulation (SCS) therapy.[2] Cost effective studies are not adequately designed to determine efficacy. Initially a screening trial needs to be performed. If certain criteria are met a permanent catheter can be considered. These criteria are; 50% pain relief, persistent pain relief during physical therapy, no additional analgesia needed and if the patient is satisfied in the effects and technical aspects of SCS.[1]

Conclusion

FBSS remains a very challenging chronic pain condition. Persistent pain, impaired function and low quality of life forms part of this clinical entity. With the increasing spinal surgery rates, the incidence of FBSS will increase. The availability of multidisciplinary treatment regimes for this condition make satisfactory outcomes possible.

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Identification and Treatment of Neuropathic Pain in Patients with Cancer

Cancer is a significant public health problem worldwide. The global burden of cancer will continue to grow because of the growth of the world's population, the aging of the population, and the increasing adoption of cancer-causing behaviors (smoking, physical inactivity, and "westernized" diets) in developing countries.[1] Based on recent estimates, about 12.7 million cancers and 7.6 million cancer deaths occurred worldwide in 2008. While incidence rates for all cancers combined in economically developed countries are nearly twice as high as in developing countries in both males and females, death rates for all cancers combined in developed countries are only 21% higher in males and only 2% higher in females. In males, lung, prostate, and colorectal cancers account for the largest percentage of new cases, and lung, liver, and stomach cancers account for the largest percentage of deaths, worldwide. In females, breast, colorectal, and cervical/uterine cancers account for the largest percentage of new cases, and breast, lung, and colorectal cancers account for the largest percentage of cancer deaths, worldwide.[1] Each of these cancers is associated with significant pain related to the disease or its treatment.

Prevalence and Undertreatment of Cancer Pain

Patients with cancer may experience acute and chronic pain as a result of their disease or its treatment, as well as pain unrelated to their cancer. In a recent systematic review of 52 studies,[2] pooled prevalence rates for cancer pain were reported for four subgroups of patients: (1) studies that included patients after curative treatment, 33% (95% confidence interval [CI] 21% to 46%); (2) studies that included patients on cancer treatment, 59% (CI 44% to 73%); (3) studies that included patients with advanced or metastatic disease, 64% (CI 58% to 69%); and (4) studies that included patients at all stages of their disease, 53% (CI 43% to 63%). Across all of the studies evaluated, approximately 33% of the patients reported pain in the moderate to severe range. These findings suggest that cancer pain is a significant problem for a large percentage of patients and that it is often undertreated. Several forms of chronic pain can be distinguished. *Somatic nociceptive pain* results from tissue damage and activation of nociceptors that innervate the skin, the ligaments, small joints, muscles, and tendons and is usually characterized by a well-localized pain. *Visceral nociceptive pain,* often characterized by colic, occurs in the hollow organs, mesenterium, capsules, and some parenchyma (e.g., the pancreas).

In addition to these nociceptive types of pain, chronic pain can also occur if the nervous system itself is damaged, which in the case of cancer may occur by tumor

infiltration of nerves, tumor-associated toxins, therapy-related toxins, or surgical damage. This type of cancer pain is called *neuropathic cancer pain.* Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."[3]

Cancer–Related Neuropathic Pain Syndromes

Common neuropathic pain syndromes are listed in Table I.

Table I Cancer-related neuropathic pain syndromes
Cancer-Related Neuropathic Pain
Paraneoplastic neurological syndromes
Tumor/metastasis infiltration or compression of the peripheral nervous system (e.g., nerves and plexuses)
Tumor/metastasis infiltration or compression of the central nervous system (e.g., spinal cord compression)
Cancer-Therapy-Induced Neuropathic Pain
Surgical interventions (e.g., postmastectomy pain)
Radiation treatment (e.g., plexopathies)
Chemotherapy-induced peripheral neuropathy (CIPN)
Cancer-Associated Neuropathic Pain
Postherpetic neuralgia

Cancer–Related Neuropathic Pain

Paraneoplastic neurological syndromes sometimes occur in association with a malignancy and are not due to the presence of metastases or direct infiltration of the cancer into the nervous system. The most frequent neurological manifestation is a peripheral neuropathy. Paraneoplastic neuropathy patients can be categorized into two groups. One group will have signs and symptoms of a predominant loss of large fibers, with dysesthesia, numbness, sensory ataxia, and sometimes pain. In the other group, a predominant loss of small fibers leads to marked neuropathic pain, often with mechanical hyperalgesia and allodynia. The diagnosis of these neurological syndromes is of particular importance because it potentially enables the early detection of the underlying malignancy.[4,5] Other cancer-related neuropathic pain syndromes result from a direct tumor/metastasis infiltration or compression of nerves and plexus (peripheral neuropathic pain) or of the central nervous system (e.g., tumor involvement of the spinal cord). One example is spinal cord compression, which occurs in approximately 5–10% of oncology patients. It is the result of metastasis to the vertebral bone or direct extension of the tumor into the epidural space. Diffuse back pain is usually the presenting symptom in spinal cord compression.[6]

Cancer Therapy–Induced Neuropathic Pain

Neuropathic pain can arise as a side effect or complication of therapeutic interventions. During surgical interventions, peripheral nerves often cannot be adequately protected. Such posttraumatic neuropathic pain syndromes develop frequently after mastectomy or thoracotomy. Chronic pain occurs in 25–50% of patients following thoracotomy and about 25–60% of patients following surgery for breast cancer.[7] Another example is phantom limb pain or stump pain. Radiotherapy—which can lead to fibrotic changes in peripheral nerves or plexuses—can induce neuropathic pain, which in some cases can begin months and years after radiation treatment. Chemotherapy-induced peripheral neuropathy (CIPN) is the most prevalent neurological complication and a major dose-limiting side effect of chemotherapeutic agents (Tables II, III). The incidence of CIPN can be variable, with estimates ranging from 10% to 100%.[8] These widely varying rates are dependent on a number of factors including the chemotherapy itself, the patient's age, the cumulative dose, dose intensity, treatment duration, coadministration of other neurotoxic drugs, and preexisting neuropathy of other origin, such as diabetes mellitus.

Neuropathic pain can arise as a side effect or complication of therapeutic interventions

CIPN can affect small and large peripheral nerve fibers. Clinical symptoms of large-fiber damage include numbness, difficulties with fine motor skills due to less of afferent feedback, decreases in sense of vibration and proprioception, and progressive loss of deep tendon reflexes. Symptoms of small-fiber loss include burning pain and decreased nociceptive and thermal perception. The pain can be so excruciating that some patients are unable to complete the optimal treatment regimen (e.g., bortezomib).

Cancer–Associated Neuropathic Pain

Acute herpes zoster is more likely to occur in cancer patients than in the general population because of the higher incidence of immunosuppression in cancer patients. Approximately 25% to 50% of patients develop postherpetic neuralgia following an acute infection.[9]

Table II Common cancer chemotherapy drugs associated with peripheral neuropathy
Bortezomib
Platinum compounds (cisplatin, carboplatin, oxaliplatin)
Taxanes (paclitaxel, docetaxel)
Thalidomide, lenalidomide
Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)

Diagnosis

As noted in a recent review,[10] there is a critical need to develop a more reliable and systematic assessment of neuropathic pain in cancer patients in order to better characterize the various types of pain and to facilitate the development and evaluation of mechanistically based therapies.

The assessment of neuropathic pain requires a detailed pain history and physical examination. The detailed pain history should include questions about onset and temporal pattern, description, location (with the use of a body map), intensity, aggravating and relieving factors, previous and current pharmacological and

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Table III
Clinical findings for chemotherapeutic substances

Chemotherapy	Sensory Findings	Pain Character	Motor Findings	Autonomic Findings	Reflexes	Recovery
Cisplatin	Paresthesia, vibration ↓, proprioception ↓, thermal sensation ?	Dysesthesia	Normal	Rare (orthostatic dysregulation)	Reduced	Some recovery, but sometimes there is progression after the end of treatment
Carboplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	
Oxaliplatin (acute)		Dysesthesia, cold allodynia, mechanical hyperalgesia	Muscle cramps	Normal	Normal	Recovery after a few days
Oxaliplatin (chronic)	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin	Similar to cisplatin
Paclitaxel, docetaxel	Paresthesia, proprioception ↓, vibration ↓, thermal and mechanical sensation ↓	Dysesthesia, burning pain, paradoxical heat sensation	Rare (proximal > distal weakness)	Rare (orthostatic dysregulation)	Reduced	Generally no recovery, and progression is possible
Vinblastine, vincristine, vindesine, vinorelbine	Proprioception ↓, vibration ↓, thermal and mechanical sensation ↓	Dysesthesia, burning, prickling pain	Distal accented weakness	Orthostatic dysregulation, constipation, impotence	Reduced	Generally after finishing treatment
Bortezomib	Proprioception ↓, vibration ↓, mechanical and thermal sensation ↓	Dysesthesia, burning, electrical pain	Rare (distal weakness)	Rare	Reduced	Generally after finishing treatment
Thalidomide	Paresthesia, proprioception ↓, vibration ↓, mechanical and thermal sensation ↓	Dysesthesia	Rare (weakness)	Rare	Reduced	?

nonpharmacological treatments and their effectiveness, and the impact of pain on function. Particular attention should be given to having patients rate the quality of their pain using standardized measures such as the McGill Pain Questionnaire[11] or the Pain Qualities Assessment Scale.[12]

There is a critical need to develop a more reliable and systematic assessment of neuropathic pain in cancer patients

Several scales have been developed to evaluate various symptoms associated with neuropathic pain, including the Leeds Assessment of Neuropathic Pain,[13] the Pain Neurotoxicity Questionnaire,[14] and painDETECT.[15] These scales include patient self-reported data, as well as various components of a physical examination. The common denominators across these questionnaires include a common set of descriptors (sensations of pins and needles, heat or burning, impaired temperature sensitivity, numbness, and electric shock-like sensations; whether or not the pain becomes worse with touch, and whether the joints are painful).[10]

A careful clinical examination is needed to support the findings from the detailed pain history.[16] Sensory testing with simple tools is an important part of the clinical examination and should include components such as touch, pinprick, pressure, cold, heat, and vibration. In addition to the sensory examination, clinicians should evaluate motor function (muscle strength and tone), deep tendon reflexes, and cranial nerve function (Table IV). Electrophysiological techniques, quantitative sensory testing, skin and nerve biopsies, and magnetic resonance imaging can be useful to help the attenuation of neuronal function and detect lesions of the central or peripheral nervous system.[17]

Management of Neuropathic Pain in Patients with Cancer

The management of nociceptive cancer pain should usually follow the World Health Organization (WHO) analgesic ladder for cancer pain relief. These guidelines can relieve 80% of nociceptive cancer pain.[18] Cancer-induced bone pain and neuropathic pain conditions are often much more difficult to treat and require

Table IV Sensory examination in clinical practice	
Sensation	Implement for Clinical Evaluation
Light touch	Cotton swab, soft brush
Pinprick, sharp pain	Wooden end of a broken cotton swab
Vibration	Tuning fork
Cold	Cold object (20°C)
Warmth	Warm object (40°C)
Reflexes	Reflex hammer

a different treatment approach. An important caveat is that most of the pharmacological and nonpharmacological interventions that are used to manage neuropathic pain in general have not been tested in patients with cancer-induced pain. An extrapolation from studies of other neuropathic pain conditions to the complicated and heterogeneous group of patients with cancer-induced neuropathic pain is far from clear.

Prevention and Management of Chemotherapy–Induced Peripheral Neuropathy

A wide variety of agents have been evaluated for the prevention and management of symptoms associated with CIPN.[8,19,20] The majority of these studies are limited by relatively small sample sizes, heterogeneous patient populations, and a lack of standardized subjective and objective outcome measures. Rigorously designed clinical trials, enrolling appropriate oncology patients in adequate numbers, using standardized measures, and including longitudinal follow-up, are needed to evaluate agents for efficacy and safety in the management of CIPN.

Rigorously designed clinical trials are needed to evaluate agents for efficacy and safety in the management of chemotherapy-induced peripheral neuropathy

Pharmacological Management of General Neuropathic Pain

The best therapeutic approach is a stepwise process to identify which drugs or drug combinations provide the greatest pain relief with the fewest side effects. Three main types of drugs (anticonvulsants, opioids, and antidepressants) and add-on medications such as topical lidocaine and capsaicin have shown consistent efficacy in clinical trials and meta-analyses on neuropathic noncancer pain.[21]

Anticonvulsants

Anticonvulsants are used in the management of neuropathic pain in patients with cancer. Probably the most widely evaluated drug is gabapentin, which has demonstrated efficacy in other neuropathic pain conditions such as diabetic neuropathy and postherpetic neuralgia.[22] Gabapentin has shown some efficacy in the management of neuropathic cancer pain.[23] However, in a Phase 3 placebo-controlled trial of patients with CIPN from platinum compounds, taxanes, and vinca alkaloids, gabapentin was not effective in reducing mean pain scores or improving patients' quality of life.[24] Additional anticonvulsants that were evaluated in the management of CIPN and failed to demonstrate efficacy include pregabalin, lamotrigine, and valproic acid.[19,20]

Opioid Analgesics

Opioid analgesics are used to manage neuropathic pain, and their efficacy has been reported in several randomized controlled trials in central and peripheral neuropathic pain.[21]

Antidepressants

Tricyclic antidepressants and selective serotonin norepinephrine reuptake inhibitors (venlafaxine and duloxetine) have demonstrated efficacy in the management of painful diabetic neuropathy and postherpetic neuralgia.[25]

Topical Treatment

Topical lidocaine (5% lidocaine patch) and a high-concentration capsaicin patch (8%) have shown efficacy and good tolerability in many studies with different types of peripheral neuropathic pain and postherpetic neuralgia.[22]

Nonpharmacological Management of Cancer–Related Neuropathic Pain

In an excellent review,[26] Cassileth and Keefe summarize the evidence for the use of massage, acupuncture, hypnosis, mirror therapy, and cognitive restructuring in the management of neuropathic pain associated with cancer. The advantages of these complementary approaches is that they are inexpensive, safe, and noninvasive, and (with the exclusion of acupuncture) they have no side effects. These techniques can be used in combination with pharmacological approaches to enhance pain management.

Summary

Neuropathic pain is a significant clinical problem in patients with cancer. It can occur as a result of the disease itself or may be associated with cancer treatment. Management of neuropathic cancer pain is different from the management of nociceptive cancer pain and requires a different treatment approach from that recommended in the WHO analgesic ladder for cancer pain relief. Most of the pharmacological and nonpharmacological interventions that are used to manage neuropathic cancer-related pain have been evaluated in other neuropathic pain conditions. Their use in neuropathic cancer-related pain was extrapolated from these studies. However, the mechanisms that underlie the development of neuropathic pain in patients with cancer may be distinct, and they warrant investigation in animal and human studies. Additional research is necessary to characterize the distinct circumstances that occur in cancer patients and to determine the most efficacious treatments for each of these neuropathic pain problems. All these scientific and clinical efforts must take into account the

special situation of patients with cancer and their potentially limited lifespan. The benefits of treatment must be carefully weighed against the patient's quality of life.

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Medication Overuse Headache

Definition

Medication overuse headache is a chronic headache that may occur in patients suffering from primary headache (especially migraine). Medication overuse is a strong risk factor for increasing headache frequency; it may worsen from an episodic headache (less than 15 headache days a month) to a chronic headache (more than 15 headache days a month over a minimum time period of 3 months).

Medication overuse can occur from too frequent intake of analgesics, compound analgesic medication, ergotamines, triptans, and opioids, if taken on a regular basis (>10 days per month). Diagnostic criteria for medication overuse headache are defined by the International Headache Society (IHS).

Epidemiology of Medication Overuse Headache

Medication overuse headache is reported all over the world. Population-based prevalence is reported to be between 0.7% and 1.7%. Prevalence varies in different countries. Medication overuse headache seems to be more frequent in women than in men (this might be due to a higher prevalence of migraine in women). Medication overuse headache is reported in up to 15% of the patients treated in specialized headache centers. Reported prevalence of medication overuse headache strongly depends on the diagnostic criteria.

The most common underlying headache disorder in medication overuse headache is migraine. Among patients presenting with a daily headache in headache centers, medication overuse headache is one of the most frequent diagnoses, suspected in up to 50% of those patients.

Risk Factors for Medication Overuse Headache

Patients with medication overuse headache are more likely to have a lower income and a lower education level compared to the general population. Frequency of medication overuse level was found to be higher in immigrants from southern or eastern European countries and within the first generation of immigrants than the second generation. The burden of headache is reported to be higher in patients with medication overuse headache resulting in decreased quality of life. Patients with other pain disorders (chronic musculoskeletal pain, rheumatic diseases) may also develop medication overuse headache due to daily intake of analgesics, especially if these patients have a history of primary headache disorder.

Pathophysiology of Medication Overuse Headache

Medication overuse headache can be caused by the intake of:

- Simple analgesics (ibuprofen, acetaminophen/paracetamol, acetylsalicylic acid, metamizol, and others)
- Ergotamines
- Compound analgesics (containing caffeine, barbiturates, and others in addition to simple analgesics)
- Triptans
- Opioids

The risk of headache development seems to be different in these substances and might be higher in ergotamines, opioids, triptans, and compound analgesics compared to simple analgesics.

The pathophysiology of medication overuse headache is not yet clearly understood. Central sensitization, genetic factors, endocrine changes, and psychological mechanisms (coping strategies, learning, and behavioral factors) may be involved.

In medication overuse headache due to substances with psychotropic effects (barbiturates, opioids, or caffeine), additional factors may play a role. However, in most cases, medication overuse is not a true addiction to substances.

Clinical Features of Medication Overuse Headache

The most common underlying headache disorder in medication overuse headache is migraine. Medication overuse headache patients report their first headache attack earlier in life than migraine patients who do not have medication overuse headache. Diagnostic criteria and differential diagnosis of medication overuse headache were provided by the IHS. The definition has changed over time, and numerous publications discuss several aspects of it. Clinical features of underlying primary headache alter when overuse continues. Headache is more bilaterally located (compared to being more unilateral in migraine). The typical pulsating pain of migraine headache may change into dull pain.

Therapy for Medication Overuse Headache

As first reported in 1951, the withdrawal of medication in patients with chronic headaches and daily intake of ergotamines reduced their headache frequency. Headache therapy thus led to the recognition of a disease that was previously unknown. Therefore, current guidelines suggest abrupt withdrawal or tapering down of overused pain medication. Inpatient withdrawal therapy is recommended for patients overusing opioids, benzodiazepine, or barbiturates because of psychotropic effects. Prophylactic therapy with substances recommended for headache prophylaxis is needed. Effects of prophylactic treatment may improve after withdrawal therapy. Corticosteroids (prednisone) may be helpful for treatment of withdrawal symptoms. Withdrawal and treatment within specialized headache centers and multidisciplinary treatment settings might be beneficial for patients with medication overuse headache.

Prognosis after Withdrawal Therapy

Relapse rate after withdrawal was up to 30% after 1 year in several studies. Therefore, after withdrawal therapy, patients should be followed up regularly to prevent a relapse of medication overuse. The relapse rate may decrease if patients are treated in multidisciplinary treatment programs. Risk factors for relapse include a high frequency of migraine after withdrawal therapy, being male, taking combination analgesics after withdrawal therapy, or taking the causative medication again after withdrawal.

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Aspen and the Health Minister cycle "from the front" for children's healthcare

Aspen Group Chief Executive, Stephen Saad, and Minister of Health Dr Aaron Motsoaledi gave new meaning to the phrase "leading from the front" when they participated in the demanding inaugural 240 kilometer Aspen Trans Karoo mountain bike challenge from Ceres to Sutherland in the Western Cape. This race is recognized as one of the most grueling in the country, by virtue of the terrain and distance that needs to be traversed.

Saad and the Minister were raising funds for the newly established Sifiso Nxasana Paediatric Trust for the Children of Africa, created by Aspen following the untimely death of Sifiso Nxasana, son of Aspen's chairwoman, Dr. Judy Dlamini and her husband Sizwe Nxasana, CEO of FirstRand Ltd.

"The Minister demonstrated his commitment to raising funds for quality healthcare for the children of South Africa in the most practical and impressive way possible," comments Saad. "He led the field of cyclists and proved his enthusiasm and passion for public-private partnerships in addressing the shortage of paediatric healthcare in our country."

"South Africa has only one paediatric hospital in comparison with Canada's 23 and Australia's 19 and that is the Red Cross Children's Hospital in Cape Town," Saad points out. "The Trust will be raising funds for the Nelson Mandela Children's Hospital and the KwaZulu Natal Children's Hospital."

The Trans Karoo race was the first phase of the fund-raising campaign and reached the encouraging sum of R10 million. "We urge both local and foreign organisations and enterprises with interests in Africa to support the Trust," says Dr Motsoaledi. "If we truly believe the children are our future then we have a responsibility to ensure that all our youngsters, irrespective of culture or background, should have access to quality paediatric care in South Africa."

The race was won by former South African Iron Man, Raynark Tissink, with Hannele Steyn being the first woman across the finishing line.

Saad completed the course in just under 16 hours, expressing the great pleasure he experienced knowing that significant results had been achieved for children's healthcare.

Dr. Aaron Motsoaledi, Minister of Health; Stephen Saad, Aspen Group Chief Executive

From left to right: Sizwe Nxasana, CEO FirstRand Ltd; Dr. Aaron Motsoaledi, Minister of Health; Dr. Judy Dlamini, Aspen Group Chairwoman; Stephen Saad, Aspen Group Chief Executive; Stavros Nicolaou, Senior Executive, Aspen Pharmacare

Pfizer announces co-promote deal with Specpharm

Described as a uniquely South African deal, Pfizer South Africa's Biopharmaceutical Division together with Specpharm announced that the no.3 ranked pharmaceutical multi-national in South Africa has contracted the services of Specpharm to co-promote a total of 22 of its pharmaceutical products within the private market. Pfizer, the US based multi-national, indicated that Specpharm was a likely match as the company exhibited a strong local presence as well as displayed the necessary expertise in the following therapeutic areas of Central Nervous System (CNS); Genitu-Urinary; Cardio-vascular (CV) and Anti-microbials.

The deal is intended to rake in revenues in the region of R120m per annum over a five year contractual period. Pfizer South Africa's Biopharmaceutical Division's CEO & Country Manager, Brian Daniel explains that this deal was carefully considered as part of enhancing Pfizer's marketing portfolio in South Africa. "Over a few months towards the latter part of 2011, a number of companies were invited to make representations to Pfizer as part of this opportunity and I am happy to announce that given Specpharm's presentation, the fit was evident."

At a specially arranged signing ceremony to announce this deal, Specpharm's Managing Director, Eugene Lottering, applauded Pfizer for its vision in this regard. "Pfizer has now provided us the opportunity to partner with a multi-national pharmaceutical giant which is intent on enhancing its local presence. Our ambition is to ensure that this five year partnership has the potential to lead to other synergies in time to come." Lottering further added: "Given Specpharm's national footprint and strong local manufacturing presence, Pfizer perceived our offering as an obvious opportunity."

As part of this deal, Pfizer will remain the dossier holders of the relevant pharmaceutical products and Specpharm has been contracted to market the 22 products on Pfizer's behalf.

"The opportunity to employ additional people as part of this initial phase is a significant benefit to both Pfizer and Specpharm. Furthermore, Pfizer will assist in the training and up-skilling of essential resources as part of this process over the period of contract. Part of this training will be centred around ensuring that Specpharm is up-skilled in the areas of adverse event reporting and Pfizer compliance systems," concluded Brian Daniel.

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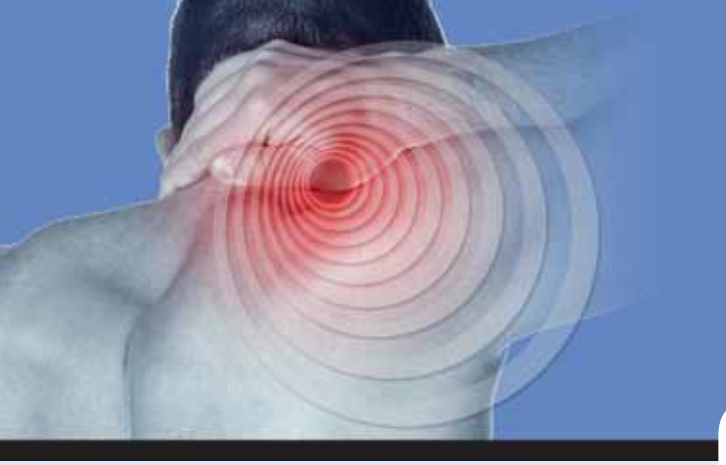
L-R: Leigh Gunkel-Keuler; Public Affairs, Policy & Communications Director, Pfizer South Africa's Biopharmaceutical Division; Jacques Mare, Business Intelligence & Development Manager, Pfizer South Africa's Biopharmaceutical Division; Karen Hulett, Established Products/Pharmacia Director, Pfizer South Africa's Biopharmaceutical Division; Brian Daniel, CEO & Country Manager, Pfizer South Africa's Biopharmaceutical Division; Dr Eugene Lottering; Managing Director, Specpharm; Nkosi Gugushe; BEE Shareholder, Specpharm; Linda Lombaard, Operations Director, Specpharm; Pieter Engelbrecht, Financial Director, Specpharm and Usheema Maraj, Marketing Manager, Specpharm

Journal of painsa

CONGRESS ISSUE 2012
PROGRAMME & ABSTRACTS



WELCOME FROM THE CHAIR OF THE ORGANISING COMMITTEE

The *PAINSA* Congress has, since its inception, developed into the premier medical education event in South Africa for health care practitioners involved in the management of patients with both acute and chronic pain.

Following in the footsteps of the very successful 2011 Pan African Pain Congress, hosted by the *PAINSA* society, in Cape Town last year, the 2012 *PAINSA* Congress promises to be just as informative and exciting. This year's Congress will be held in the nation's capital (Pretoria) at the CSIR Convention Centre from the 22nd to 24th June. In addition to the excellent Congress Academic Programme, there will also be two pre-congress workshops, in addition to the breakfast symposium on Saturday morning and the two industrial symposiums during the Congress.

The Congress Scientific Committee, under the leadership of Professor Peter Kamerman, has brought together an impressive group of leaders in the field of pain medicine, to create the most comprehensive programme of pain education this Congress has ever seen.

Over and above the excellent academic content available, delegates will also have an opportunity to interact with the large trade contingent that will be present at the Congress, at the opening cocktail party on Friday 22nd June 2012. The large commitment at this Congress from the medical drug and device industry is testament to the important role that the annual *PAINSA* Congress plays in the field of pain medicine in South Africa.

On behalf of the 2012 *PAINSA* Congress local organizing committee it will give me great pleasure to welcome you to Pretoria in June 2012.

I hope you will find that meeting to be beneficial to your clinical practice, and hopefully will result in more patients becoming pain free.

Best regards,
Dr Sean Chetty
MBChB, DCH(SA), DA(SA), FCA(SA), Cert Crit Care(SA)
CHAIR: ORGANISING COMMITTEE

WELCOME FROM THE SCIENTIFIC PROGRAMME COMMITTEE

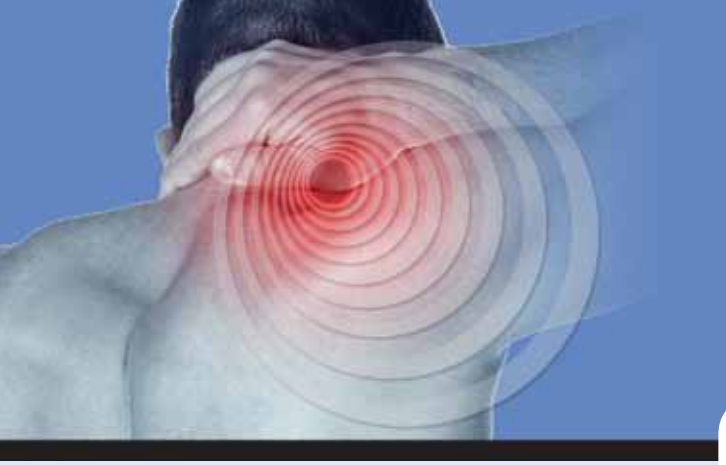
Welcome to the 2012 Congress of *PAINSA*. The Congress has developed into the premier Congress in the field of pain in South Africa based largely on the strong scientific programme presented at our meetings. We take care when developing the scientific programme to follow the guiding principles of our parent body, the International Association for the Study of Pain (IASP), and deliver content that is multidisciplinary in nature and which strikes a balance between clinical science and basic science.

For the 2012 Congress, the scientific programme is based around eight themed sessions, which include seven clinical sessions (sports injuries, painful arthrides, neuropathic pain, headaches, lowback pain, acute pain, psychosocial aspects of pain), and one basic science session. In addition, there is a CPD-accredited ethics presentation on the ethics of pain management, and a session dedicated to free communications, where local researchers will present their latest research findings. We are especially encouraged by the growth in the number and quality of the submissions to the free communication session, and we hope that you will come support our local pain researchers, because it is only through research that we will gain an understanding of pain and its management in South Africa.

In each clinical session, national and international experts will provide delegates with insights into clinical practices that will improve your diagnosis and management of common pain conditions, with dedicated time at the end of each session for open discussion between the speakers and the audience. A core feature of the programme is the emphasis on multimodal pain management.

Throughout this Conference, I ask you to stay engaged, be proactive, and help us improve pain management in South Africa.

Best regards,
Dr Peter Kamerman, PhD
CHAIR: SCIENTIFIC PROGRAMME COMMITTEE

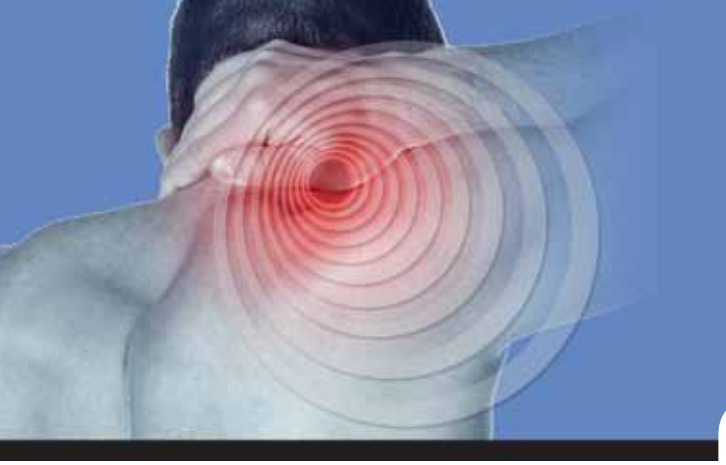


PROGRAMME

PAIN SA CONGRESS 2012 / SCIENTIFIC PROGRAMME		
FRIDAY 22 JUNE: PRE-CONGRESS WORKSHOPS		
10h00 - 11h00	Registration opens	
11h00 - 13h00	Pre-Congress Workshops	
	Workshop 1:	Workshop 2 :
	Training the brain for pathological pain: graded motor imagery and other fun treatments Prof Lorimer Moseley	Regional anaesthesia ultrasound workshop
13h00 - 14h00	**Lunch**	
	Workshop 1 continued	Workshop 2 continued
16h00 - 16h30	**Tea / Coffee break**	
	Workshop 1 continued	Workshop 2 continued
18h00	**Cocktail function in the exhibition area**	
SATURDAY 23 JUNE		
07h00 - 08h00	**Breakfast Symposium: New Treatment in Pain Management (sponsored by Janssen Pharmaceuticals)**	
07h30 - 08h10	Registration opens	
08h10 - 08h20	Congress Opening	
	Plenary Lecture **Chairperson: Dr Sean Chetty**	
08h20 - 09h00	The brain in pain: current concepts and opportunities	Prof Lorimer Moseley
	Biopsychosocial Session **Chairperson: Dr Sean Chetty**	
09h00 - 09h15	Biopsychosocial model of chronic pain	Mrs Bev Bolton
09h15 - 09h30	The use of group therapy in pain management	Mrs Christa du Toit
09h30 - 09h45	Psychiatric disease and pain	Dr Anusha Lachman
09h45 - 10h00	Biopsychosocial discussion	
10h00 - 10h30	**Tea / Coffee break**	
	Basic Science Industrial Symposium (sponsored by Janssen Pharmaceuticals) **Chairperson: Prof Helgard Meyer**	
10h30 - 10h46	Where do analgesic medications work?	Prof Peter Kamerman
10h46 - 11h03	Opiophobia	Prof Duncan Mitchell
11h03 - 11h20	Genetics of pain	Mrs Antonia Wadley
11h20 - 11h30	Basic Science discussion	
	Acute Pain Session **Chairperson: Dr Milton Raff**	
11h30 - 11h45	Regional anaesthesia: why and when should you employ regional nerve blocks	Dr Eric Hodgson
11h45 - 12h00	Patient-controlled analgesia	Dr Janieke van Nugteren
12h00 - 12h15	Acute postoperative pain management: life after dextropropoxyphene	Prof Eva Frohlich
12h15 - 12h30	Acute pain management discussion	
12h30 - 14h00	**Lunch in the Exhibition Centre**	

	Low Back Pain Session **Chairperson: Dr Eric Hodgson**	
14h00 - 14h15	Aetiology of chronic low back pain: identifying pain generators	Prof Duncan Mitchell
14h15 - 14h30	Low back pain - a primary care approach	Prof Helgard Meyer
14h30 - 14h45	Non-pharmacological management of low back pain	Ms Romy Parker
14h45 - 15h00	Surgical interventions for low back pain	Dr Kobus Steyn
15h00 - 15h15	Minor non-surgical interventions for low back pain	Dr Pauline du Plessis
15h15 - 15h30	Low back pain discussion	
15h30 - 16h00	**Tea / Coffee break**	
	Free Communications **Chairperson: Ms Romy Parker**	
16h00 - 16h15	Association of unique polymorphisms in KCNS1 with Neuropathic pain sensitivity in african individuals with HIV-associated sensory neuropathy	Ms Liesl Hendry
16h15 - 16h30	HIV-positive patients with a pre-existing neuropathy may initially experience an increase in symptom severity, however, after six months of stavudine-based therapy, a small percentage do experience symptom relief.	Ms Prinisha Pillay
16h30 - 16h45	Is postoperative hypernociception associated with anxiety-like behaviour in rats?	Ms Stephanie Ferreira
16h45 - 17h00	The prevalence of chronic pain and its impact on patients attending primary healthcare facilities in South West Tshwane, South Africa	Dr WN Rauf
17h00 - 17h15	Sports physiotherapists' knowledge, attitudes and beliefs of pain: preliminary results from a cross-sectional correlational study	Ms Nadia Clenzos
17h15 - 17h30	Cervico-mandibular muscle activity in females with chronic cervical pain: a descriptive, cross-sectional, correlational study	Ms Patricia Lang
17h30 - 17h45	The prevalence of chronic postmastectomy pain syndrome (PMPS) in female breast cancer survivors	Dr Muhammed Variawa
17h45 - 18h00	The prevalence of work-related musculoskeletal pain complaints among general surgeons	Ms FA Desai
18h00 - 18h30	**Pain SA AGM**	

SUNDAY 24 JUNE		
07h30 - 08h30	Registration opens	
	Sports Injury Industrial Symposium (Sponsored by: Pfizer) **Chairperson: A/Prof Peter Kamerman**	
08h30 - 08h50	Pain, using the sports medicine model	Prof Demitri Constantinou
08h50 - 09h10	Pharmacological management of pain associated with sports injuries	Dr Glen Hagemann
09h10 - 09h30	Non-pharmacological management of pain associated with sports injuries	Ms Romy Parker
09h30 - 09h50	Sports injuries discussion	
	Headache Session **Chairperson: Prof Duncan Mitchell**	
09h50 - 10h05	Diagnosis and treatment of tension-type headaches	Dr Ina Diener
10h05 - 10h20	Diagnosis and treatment of migraine	Dr Johan Smuts
10h20 - 10h35	Headache discussion	
10h35 - 11h00	**Tea / Coffee break**	
	Neuropathic Pain Session **Chairperson: Dr Johan Smuts**	
11h00 - 11h15	Diagnosis of neuropathic pain in the primary care setting	Prof Ahmed Bhigjee
11h15 - 11h30	South African neuropathic pain management guidelines	Dr Sean Chetty
11h30 - 11h45	Neuropathic pain discussion	
	Inflammatory Arthritides Session **Chairperson: Prof Eva Frohlich**	
11h45 - 12h05	Diagnosis of chronic inflammatory arthritides	Dr Berenice Christian
12h05 - 12h25	Pharmacological management of chronic inflammatory arthritides	Prof Mohammed Tikly
12h25 - 12h45	Non-pharmacological management of chronic inflammatory arthritides	Ms Dershnee Devan
12h45 - 13h00	Inflammatory arthritides discussion	
	Ethics **Chairperson: Prof Eva Frohlich**	
13h00 - 13h30	Pain management... a human right?	Dr Milton Raff
13h30 - 13h35	**Closing**	
13h35	**Lunch**	



FREE COMMUNICATION ABSTRACTS

ASSOCIATION OF UNIQUE POLYMORPHISMS IN *KCNS1* WITH NEUROPATHIC PAIN SENSITIVITY IN AFRICAN INDIVIDUALS WITH HIV-ASSOCIATED SENSORY NEUROPATHY

Liesl Hendry[1,2], Antonia Wadley[2], Peter Kamerman[2], Zané Lombard[1]

[1]Division of Human Genetics, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand/National Health Laboratory Service;[2] Brain Function Research Group, School of Physiology, University of the Witwatersrand

Background: Antiretroviral toxic neuropathy (ATN) is a common neurological complication of HIV infection and its treatment, and typically is painful. A single nucleotide polymorphism (SNP) within the *KCNS1* gene, which encodes a voltage-gated potassium channel, has been associated with pain intensity for several neuropathic pain conditions in non-African populations. The investigation aimed to assess the association between this previously identified SNP, and population-specific tagSNPs, in *KCNS1* and pain intensity in a Black African population with ATN.

Methods: DNA was isolated from 158 HIV-positive Black South African individuals of 18 years or older. All participants had a clinical diagnosis of ATN and a confirmed HIV infection; and had been on stavudine-based antiretroviral therapy for at least six months. SNP selection was based on the SNP identified in the literature (rs734784), and supplemented with tagSNPs appropriate for an African population. The Tagger algorithm was used to select tagSNPs in a pairwise approach at $r^2 > 1.0$ and minor allele frequency (MAF) > 0.01 among publicly available African data (Yoruba population, YRI) from the International HapMap dataset. TagSNP selection produced three additional SNPs for investigation (rs4499491, rs6017486 and rs6073643). Genotyping was carried out using a GoldenGateTM Genotyping Assay with VeraCode microbeads and data was read on an Illumina BeadXpress Reader. Analysis was performed using PLINK software for association analysis.

Results: None of the SNPs alone associated with pain intensity. Upon random construction of haplotypes, four haplotypes, none of which include the literature SNP rs734784, correlated to differences in pain intensity on univariate analysis and on multivariate analysis (correcting for age, gender and CD4 T-cell count).

Conclusion: The investigation suggests that haplotypes consisting of population-specific polymorphisms in *KCNS1* influence pain intensity in this group of African subjects. Our data support data from non-African populations demonstrating a role for *KCNS1* in neuropathic pain.

SYMPTOM CHANGES AFTER STARTING ANTIRETROVIRAL THERAPY IN HIV-PATIENTS WITH PRE-EXISTING PERIPHERAL NEUROPATHY.

Prinisha Pillay, Antonia Wadley, Peter Kamerman

Brain Function Research Group, School of Physiology, University of the Witwatersrand

Background: Sensory neuropathy is a common complication of HIV-infection and its treatment. Whilst, several studies have linked stavudine-based therapy to the development of neuropathy, very few have examined the change in pre-existing symptoms of neuropathy in patients initiating antiretroviral therapy. We investigated whether initiating stavudine-based combination antiretroviral therapy improved the symptoms of HIV-positive patients who had a pre-existing symptomatic neuropathy.

Methods: Thirteen (3 female, 10 male) HIV-positive patients who presented with a pre-existing symptomatic neuropathy were enrolled into the study. The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (protocol number: M090671). Patients were recruited at the Greenhouse Pharmacy of the Chris-Hani Baragwanath Hospital and were screened using the AIDS Clinical Trials Group neuropathy screening tool. Peripheral sensory neuropathy was identified by the bilateral presence of at least one sign (decreased vibration sense in great toe or absent ankle reflex) and one symptom (pain, paraesthesia or numbness) in the feet.

Results: Five patients were lost to follow-up over the six-month period. The most common symptom experienced at baseline was numbness 75% (6/8), and 37% (3/8) patients had a combination of all three symptoms: pain, numbness and pins and needles. By three months of follow-up, 63% (5/8) patients had a combination of all three symptoms. The only symptom that decreased significantly (in severity) over the six-month period was numbness (p=0.006). Seven (88%) patients received analgesic treatment for symptom relief and amitriptyline was the most common analgesic prescribed either alone 57% (4/7) or in combination with codeine 14% (1/7) or codeine and ibuprofen 14% (1/7).

Conclusion: HIV-positive patients with a pre-existing neuropathy may initially experience an increase in symptom severity, however, after six months of stavudine-based therapy, a small percentage do experience symptom relief.

IS POSTOPERATIVE HYPERNOCICEPTION ASSOCIATED WITH ANXIETY-LIKE BEHAVIOUR IN RATS?

Stephanie Ferreira, Tanya Swanepoel, Peter Kamerman

Brain Function Research Group, School of Physiology, University of the Witwatersrand

Background: Existing animal models of postoperative pain have focused on the sensory aspects of postoperative nociception, and have ignored the affective components of pain, such as anxiety, which in human studies have been shown to be important determinants of the overall pain experience and pain outcomes. Therefore we investigated whether anxiety-like behaviour was a feature of an established animal model of postoperative pain.

Methods: Postoperative hypernociception was assessed on a daily basis prior to surgery and nine days after surgery in 10 male Sprague-Dawley rats, that had an incision made through the abdominal wall. Nociceptive thresholds were tested using an anaesthesiometer, which was applied to the wound until the rats showed aversive responses. Anxiety-like behaviour was assessed in a separate group of 50 experimental and 50 control rats that had undergone the same surgical intervention or sham surgery (anaesthesia only). The open field paradigm was used to test anxiety-like behaviour, and involved placing rats in a 1 m2 arena and measuring their exploratory behaviour; behaviour that is reduced in anxious rats. An additional 50 experimental and 50 control rats were decapitated and trunk blood was collected for corticosterone measurement, and the prefrontal cortex and hippocampus were excised for measurement of serotonin, noradrenaline, dopamine, GABA and glutamate.

Results: Surgery produced a significant decrease in nociceptive thresholds for up to six days after postoperatively, however there was no significant difference between control and surgery rats with regards to exploratory behaviour of a novel environment at any stage after surgery. There was no significant difference between any of the monoamines, GABA, glutamate or corticosterone levels between the surgery and control groups, on any of the postoperative days.

Conclusion: Therefore rats do not display anxiety-like behaviour, or express circulating or brain biomarkers of stress, in an established model of postoperative pain.

THE PREVALENCE OF CHRONIC PAIN AND ITS IMPACT ON PATIENTS ATTENDING PRIMARY HEALTHCARE FACILITIES IN SOUTH WEST TSHWANE, SOUTH AFRICA

WN Rauf, HP Meyer

Department of Family Medicine, Faculty of Health Sciences, University of Pretoria

Background: Despite the worldwide high prevalence of chronic pain and the significance of chronic pain as a healthcare problem, no published data are available on the prevalence and impact of chronic pain in the South African primary healthcare context.

Methods: A prospective, cross-sectional study was carried out in four primary healthcare clinics, situated in south-west Tshwane, South Africa. The study was conducted on a total of 1066 adult patients (aged 18 years or older), over a nine-week period between October and December 2010. The prevalence of chronic pain was determined and patients with chronic pain were invited to complete the Wisconsin Brief Pain Questionnaire (BPI), an interviewer-administered questionnaire to assess the impact of the pain.

Results: Chronic pain prevalence was 41%; Confidence Interval [CI]: 37.2%; 45.6%. Chronic pain was most frequently experienced as lower backache pain [prevalence 30.83% (CI: 19.56; 42.09)] and joint pains [prevalence 23.48% (CI: 7.58; 39.38)]. Chronic pain was significantly more prevalent with advancing age (P=0.0014), in women as compared to the men (P=0.019), and in widowed and divorced as compared to married and single (P=0.0062) patients. A large proportion of chronic pain patients reported negative impacts of chronic pain on their mood: 75.89% (95% CI: 60.42%; 86.65%); interpersonal relationships: 69.16% (95% CI: 50.38%; 83.21%); walking ability: 81.53% (95% CI: 70.09%; 89.26%); sleep quality: 83.72% (95% CI: 71.26%; 91.43%), routine house work: 83.12% (95% CI: 69.52%; 91.40%) and enjoyment of life: 80.12% (95% CI: 64.51%;89.94%). The increase in pain intensity was significantly associated with more negative impact on the quality of life of the patients.

Conclusion: Chronic pain is highly prevalent in patients attending primary health care facilities in the south-west Tshwane area. A large proportion of chronic pain patients are experiencing negative bio-psychosocial impacts of chronic pain in their lives.

SPORTS PHYSIOTHERAPISTS' KNOWLEDGE, ATTITUDES AND BELIEFS OF PAIN: PRELIMINARY RESULTS FROM A CROSS-SECTIONAL CORRELATIONAL STUDY

Nadia Clenzos, Romy Parker, Niri Naidoo

Department of Health and Rehabilitation Sciences, University of Cape Town

Background: Pain is the most common complaint for which patients seek the help of a physiotherapist. Previous studies have found deficits in pain knowledge, attitudes and beliefs among health care providers. Poor knowledge and negative attitudes about pain are recognised to lead to poor assessment ability and subsequent poor pain management. Aim: The purpose of this study was to investigate the pain knowledge, pain attitudes and pain beliefs of physiotherapists treating athletes and to explore factors which may contribute to level of knowledge or influence attitudes and beliefs

Methods: Data was collected by means of an online questionnaire, which included a demographic questionnaire and Unruh's Revised Pain Knowledge and Attitudes Questionnaire (RPKAQ). Participants were members of the Sports Physiotherapy Group and Orthopaedic Manipulative Physiotherapy Group of the South African Society of Physiotherapy. Two hundred and seven physiotherapists completed the questionnaire.

Results: The mean score for the RPKAQ was 65.53%. 14.49% (n=30) of the physiotherapists scored 75% or above. Lowest scores were obtained for the 'Assessment and Measurement of Pain' (47.73%) and 'Developmental Changes in Pain Perception' (58.32%) sections of the RPKAQ. The highest mean score was obtained for the 'Physiological Basis of Pain' (76.43%) section of the RPKAQ.

Conclusion: There is an inadequate level of pain knowledge among sports physiotherapists in South Africa, particularly in the areas of assessment and measurement of pain and developmental changes in pain perception. Clinical relevance: The identification of areas that are lacking would allow the implementation of an evidence-based intervention strategy aimed at improving physiotherapists' awareness, knowledge and assessment of pain. Adequate knowledge of pain and ability to assess pain is essential in order to treat appropriately, effectively and optimally.

CERVICO-MANDIBULAR MUSCLE ACTIVITY IN FEMALES WITH CHRONIC CERVICAL PAIN: A DESCRIPTIVE, CROSS-SECTIONAL, CORRELATIONAL STUDY

Patricia Lang, Romy Parker, Theresa Burgess

Department of Health and Rehabilitation Sciences, University of Cape Town

Background: Pathophysiological mechanisms behind chronic cervical musculoskeletal conditions in office workers remain unclear. Hence, the study aim was to explore cervico-mandibular muscle activity levels in females with chronic cervical musculoskeletal conditions, who showed no symptoms of temporomandibular disorders.

Methods: A descriptive cross-sectional correlational design. Participants were administered five validated questionnaires (Research Diagnostic Criteria for TMD, Neck Disability Index, Computer Usage Questionnaire, Brief Pain Inventory, EuroQol-5D), for categorisation and comparison of case (n = 20) and control group (n = 22) socio-demographic and biopsychosocial variables. Surface electromyographic cervico-mandibular activity was recorded in 10 second epochs in the sitting position at rest and during first posterior tooth contact (light clench).

Results: The case group had higher scores than the control group for cervical disability ($p < 0.01$), pain ($p < 0.01$), presence of a daytime teeth clenching habit ($p = 0.01$), and health related quality of life sub-sections of pain ($p < 0.01$) and anxiety/depression ($p = 0.05$), and lower scores for perceived health status ($p = 0.02$). No differences in cervico-mandibular activity level at rest or during light clench were found between groups. Relationships existed between cervical disability and pain for the total sample (Rho = 0.80; $p < 0.05$), case (Rho = 0.72; $p < 0.05$), and control group (Rho = 0.50; $p < 0.05$), and between cervical disability and health status for the total sample (Rho = -0.35; $p < 0.05$). No relationship existed between cervical disability and resting cervico-mandibular electrical activity for the total sample, case, or control group. Using teeth clenching as a grouping variable, differences were found between groups for cervical disability ($p = 0.02$), and health related quality of life sub-sections of pain ($p = 0.02$) and anxiety/depression ($p < 0.01$). Using anxiety/depression as a grouping variable, differences were found between groups for cervical disability ($p = 0.01$), pain ($p < 0.01$), state of health ($p = 0.01$) and teeth clenching habits ($p < 0.01$).

Conclusion: Interactive relationships between cervical disability, the presence of teeth clenching, and anxiety/depression allude to significant pathophysiological mechanisms of central sensitisation and central nervous system changes and drivers that underlie chronic cervical pain, not limited to the physical nociceptive system. Recommendations include the need to address cervical disability, teeth clenching, and anxiety/depression in the clinician' approach toward chronic cervical musculoskeletal conditions.

THE PREVALENCE OF CHRONIC POSTMASTECTOMY PAIN SYNDROME (PMPS) IN FEMALE BREAST CANCER SURVIVORS

Muhammed Luqmaan Variawa, Sean Chetty, Juan Scribante

Department of Anaesthesiology, School of Clinical Medicine, University of the Witwatersrand

Background: Breast cancer is one of the most common cancer diagnoses in women and is a significant cause of mortality and morbidity worldwide. Surgical treatment is indicated in most patients. Postmastectomy pain syndrome (PMPS) is a persistent and debilitating neuropathic pain syndrome that develops after breast surgery, but there are no studies determining the prevalence of PMPS in South Africa. A detailed description of the prevalence of PMPS is needed to understand the problem in this patient group which may enable the development of a more effective pain management strategy. The objectives of this study were to determine the prevalence of postmastectomy pain syndrome in adult female breast cancer patients following general anaesthesia without regional anaesthesia. Methods: The research design was that of a cross-sectional descriptive survey study assessing chronic pain in breast cancer survivors at Chris Hani Baragwanath Hospital. Johannesburg. The validated DN4 pain questionnaire, including demographic and clinical data, was used in this study. Data was obtained by examining the patients` medical records and reviewing the patient database at the breast clinic. An average prevalence estimation of 35% was used to statistically calculate the sample size. A convenience sample of women were recruited and interviewed when returning to the breast surgery clinic for routine follow-up examinations.

Results: The study included 95 patients. The prevalence of PMPS in this study was found to be 36.84% (n=35). The average DN4 pain score was 5.97 in this group. Three patients (3.2%) reported non-neuropathic chronic postoperative pain. The average age of patients interviewed was 57.96 years (range 30 to 90 years). The average duration that patients experienced neuropathic pain symptoms was 12.22 months. Of the patients with PMPS, one (2.9%) received radiotherapy alone, 9 (25.71%) received chemotherapy alone and 12 (34.29%) received chemo-radiation therapy as part of their treatment regime. Thirteen patients (37.14%) with PMPS received no chemo-radiation therapy. The majority of patients were using simple analgesic medications for pain relief.

Conclusion: Even though surgical procedures are becoming less invasive, the high prevalence of PMPS after treatment for breast cancer remains a clinically significant problem. This necessitates the development of more effective prevention and treatment strategies for this syndrome to improve patients' quality of life.

THE PREVALENCE OF WORK-RELATED MUSCULOSKELETAL PAIN COMPLAINTS AMONG GENERAL SURGEONS

FA Desai, TJ Elanpen, HJ van Heerden

Faculty of Health Science, University of KwaZulu-Natal

Background: During surgery, surgeons experienced substantial stress to the musculoskeletal system. The proposed aetiology of such stress has been attributed to a large number of ergonomic variables. International data suggests musculoskleetal pain is significantly prevalent among surgeons. The aim of this study was to investigate the prevalence of musculoskeletal pain complaints and their possible aetiology among general surgeons in the South African context.

Methods: Seventy six general surgeons participated in an occupational, epidemiological, retrospective study, voluntarily. Biographical and kinanthropometric measurements, occupational and musculoskeletal information were gathered using a self-report questionnaire (n=76). Critical to the occupational data gathered was: times spent performing surgery, type of surgical procedure employed and the various ergonomic postures employed (cervical, glenohumeral, vertebral and elbow inclination). Results from the questionnaires were captured on a Statistical Package for Social Sciences (SPSS) with the probability set at 0.05.

Results: According to the results, 69.74% of the cohort experienced musculoskeletal pain in one or more anatomical location/s (n=53) ($p<0.001$) of which lower back pain (60.38%) was the most prevalent ($p<0.01$). The majority (n=76) of the cohort opted for standing posture with prolonged, sustained cervical, vertebral, glenohumeral and elbow flexion during surgical procedures Preference to stand (n=76) or remain seated (n=71) during a surgical procedure is postulated to be a non significant aetiological factor as both these portions of the cohort experienced a similar prevalence of musculoskeletal pain (69.73% vs. 67.61%; $p>0.05$).

Conclusion: Disadvantageous ergonomic practices such as; prolonged seated and standing postures, repetitive hand movements, awkward body postures and strenuous vertebral and glenohumeral positions are postulated to be aetiological factors influencing the development of work-related musculoskeletal pain and symptoms among this cohort. Surgeons seldom receive specialised training on the optimum postures to be employed during surgical procedures. This leaves general surgeons vulnerable to physical loads imposed on them in the operating room, further exacerbating their exposure to musculoskeletal pain.

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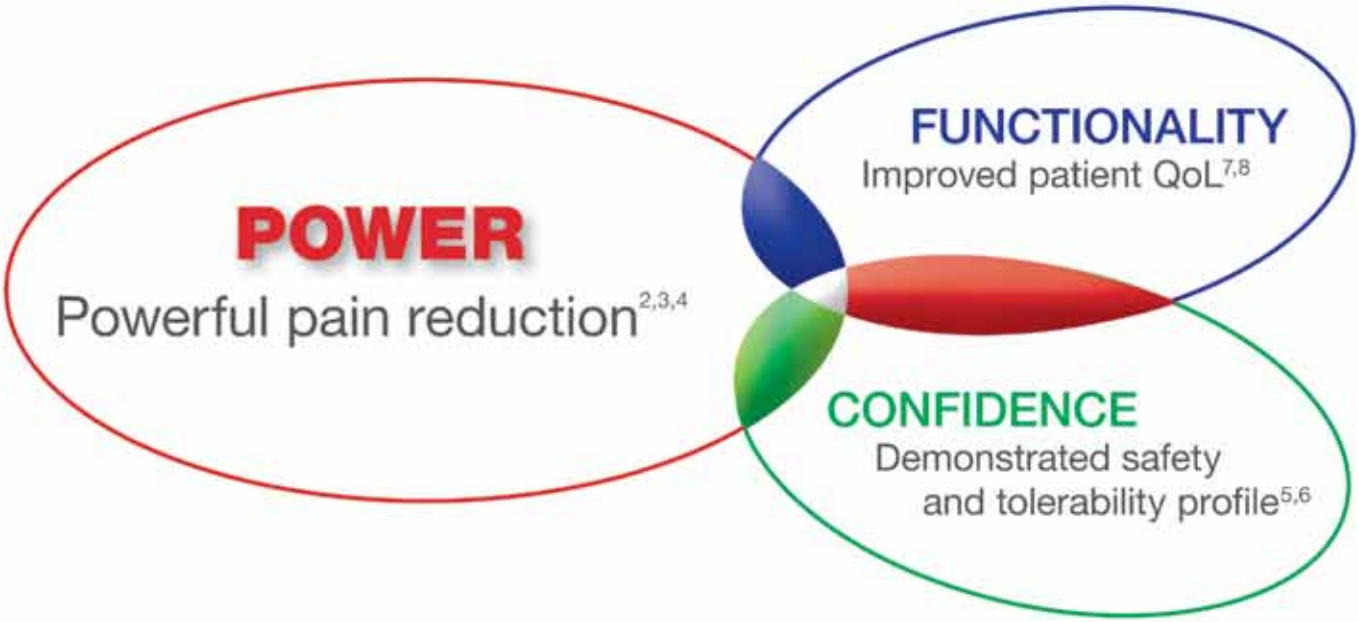

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References: 1. Celebrex prescribing information. (PI ref: 11/12/2008). **2.** Frampton JE, Keating GM. Celecoxib: A Review of its Use in the Management of Arthritis and Acute Pain. *Drugs* 2007;67(16):2433-2472. **3.** Petri M, Hufman SL, Waser G, Cui H, Snabes MC, Verburg KM. Celecoxib effectively treats patients with acute shoulder tendinitis/bursitis. *J Rheumatol* 2004;31(8):1614-1621. **4.** Derry S, Barden J, McQuay HJ, Moore RA. Single dose oral celecoxib for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2008;(4):CD004233. **5.** Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: a randomized, controlled trial. *J Clin Pharmacol* 2000;40:124-132. **6.** Nadarajah A, Abrahan L, Lau FL, Hwang LJ, Fakir-Bolte C. Efficacy and tolerability of celecoxib compared with diclofenac slow release in the treatment of acute ankle sprain in an Asian population. *Singapore Med J* 2006;47(6):534-542. **7.** Zhao SZ, McMillen JI, Markenson JA, Dedhiya SD, Zhao WW, Osterhaus JT *et al.* Evaluation of the Functional Status Aspects of Health-Related Quality of Life of Patients with Osteoarthritis Treated with Celecoxib. *Pharmacotherapy* 1999;19(11):1269-1278. **8.** Rozenberg S, Meric G, Jeanpetit Y. [Changes in quality of life in patients with osteoarthritis treated with celecoxib: the Qualice study.] *Presse Med* 2008;37:571-578.

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